Department of Ophthalmology, Faculty of Medicine
University of Helsinki and Helsinki University Hospital
Doctoral Programme in Clinical Research

Risk factors for wet age-related macular degeneration

- Effects of treatment of cataract and posterior capsular opacification and injection care (protocols) on wet age-related macular degeneration in a Finnish population including the association of periodontitis with wet age-related macular degeneration.

Petteri Karesvuo MD

DOCTORAL DISSERTATION

To be presented for public discussion with the permission of the Faculty of Medicine of the University of Helsinki, in Auditorium 2, at Biomedicum, on the 5th of November 2021 at 13.00.

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To my family,

Minna, Sylvia, Pietari & Martta

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LIST OF ORIGINAL PUBLICATIONS

These are referred to in the text by their Roman numerals:

I Karesvuo P, Gursoy UK, Pussinen PJ, Suominen AL, Huumonen S, Vesti E, Könönen E. Alveolar bone loss associated with age-related macular degeneration in males. Journal of Periodontology 2013 Jan;84(1):58-67.

II Karesvuo P, Hakkala L, Kaarniranta K, Uusitalo H, Ojamo M, and Tuuminen R. Correlation between the rate of intravitreal injections, use of aflibercept as a second-line treatment and visual impairment for wet AMD in Finland. Acta Ophthalmologica 2020 Feb 24. Online ahead of print.

III Hecht I, Karesvuo P, Achiron A, Elbaz U, Laine I, Tuuminen R. Anti-inflammatory medication after cataract surgery and posterior capsular opacification. American Journal of Ophthalmology 2020 Feb 13. Online ahead of print.

IV Karesvuo P, Elbaz U, Achiron A,, Hecht I, Kaarniranta K, Tuuminen R. Effect of cataract surgery on wet age-related macular degeneration activity. Acta Ophthalmologica 2021, Apr 10. Online ahead of print.

V Hecht I, Dubinsky-Pertzov B, Karesvuo P, Achiron A, Tuuminen R. Association between Intraocular lens diopter and posterior capsular opacification. Clin Exp Ophthalmol 2020, Jul 8. Ahead of print.

VI Achiron A, Elbaz U, Hecht I, Spierer O, Einan-Lifshitz A, Karesvuo P, Tuuminen R. The Effect of Blue-Light Filtering Intraocular Lenses on the Development and Progression of Neovascular Age-Related Macular Degeneration. Ophthalmology 2021, Mar; 128(3):410-416. Epub 2020 Jul 24.

ABBREVIATIONS

AMD	age-related macular degeneration
anti-VEGF	anti-vascular endothelial growth factor
aMMP-8	active matrix metalloproteinase-8
AREDS	Age-Related Eye Disease Study
ARM	age-related maculopathy
ARMD	age-related macular degeneration
BCVA	best corrected visual acuity
BMI	body mass index
BOP	bleeding on probing
BP	blood pressure
BRVO	branch retinal venous occlusion
BSS	balanced salt solution
CF	color fundus photography
CFH	complement factor H
CME	cystic macular edema
CNV	choroidal neovascularization
CRP	C-reactive protein
CRVO	central retinal venous occlusion
CSC	central serous chorioretinopathy
CSMT	central subfield macular thickness
DNA	deoxyribonucleic acid
ECCE	extracapsular cataract extraction
ERM	epiretinal membrane
FA	fluorescein angiography

GA	geographic atrophy
HDL	high-density lipoprotein
hsCRP	high-sensitivity c-reactive protein
ICCE	intracapsular cataract extraction
ICG	indocyanine green
IL-6	interleukin-6
IL-8	interleukin-8
IOL	intraocular lens
ICAM-1	intercellular adhesion molecule 1
KTL	National Institute for Health and Welfare, formerly Finnish National Public Health Institute
LDL	low-density lipoprotein
LMT	limited macular translocation surgery
LPS	lipopolysaccharide
MCP-1	monocyte chemoattractant protein 1
MNV	macular neovascularization
mCRP	monomeric CRP
NED	neuroepithelial detachment
OCT	optical coherence tomography
OCT-A	OCT angiography
OPG	orthopantomogram
PCO	posterior capsular opacification
PIOL	phakic intraocular lens
pCRP	pentameric CRP
PCV	polypoidal choroidal vasculopathy
PCR	polymerase chain reaction

PED	pigment epithelial detachment
PNV	pachychoroid neovasculopathy
PPE	pachychoroid pigment epitheliopathy
PRN	pro re nata
PSCC	posterior subcapsular cataract
RAP	retinal angiomatous proliferation
RNFL	retinal nerve fiber layer
ROP	retinopathy of prematurity
RPE	retinal pigment epithelium
r-tPA	recombinant tissue plasminogen activator
SHRM	subretinal hyperreflective material
QoL	quality of life
TER	treat and extend
TNF-α	tumor necrosis factor alpha
TLR	toll-like receptor
VCAM-1	vascular cell adhesion molecule 1
VEGF	vascular endothelial growth factor
VEP	visual evoked potential
WHO	World Health Organization

Abstract

Age-related macular degeneration is the leading cause of visual impairment in developed countries. It is divided into two forms, dry and wet. The etiology of the diseases is still not fully understood. Known risk factors include advanced age, genetics and tobacco smoking. New candidates like Helicobacter pylori, Cytomegalovirus, Chlamydia pneumoniae have been studied but without strong evidence of any association. Low-grade inflammation caused by obesity, for example, places a burden on the eye. We studied one known infection of the tissue supporting the teeth, periodontitis, and its effect on AMD. Surprisingly we found an association between these two diseases in males.

Age-related cataract is the leading cause of visual impairment and blindness in developing countries. Cataract operation is one of the commonest procedures in medicine. It brings light to elderly people and greatly improves vision and quality of life. However, there are known complications like posterior capsule opacification (PCO), which puts a burden on healthcare providers and patients alike. Postoperative topical medication is widely used after a cataract operation and drugs are being studied to provide optimal relief of postoperative complications. In our study we found that postoperative topical steroid reduced PCO more effectively than topical NSAID drops.

Cataract operations are performed using different types of intraocular lenses (IOL), namely low, intermediate and high diopter IOLs. These lenses can be divided into blue light filtering IOLs and non-blue light filtering IOLs. In animal models blue light has been found to be harmful to the retina, and after the operation there is no longer a crystalline lens to provide protection. The lenses are designed to take this into account and help to protect against wet AMD. We found in our study that low diopter IOLs resulted in more PCO than higher diopter IOLs. We also found no difference between blue light filtering IOLs and non-blue light filtering IOLs in terms of new-onset wet AMD cases.

Age-related macular degeneration and cataract often co-exist. The cataract operation induces a small amount of inflammation in the eye and it has been found, albeit with differing results, that cataract operations could activate wet age-related macular degeneration. In our study we found that a cataract operation did not affect wet AMD, its progression or the number of injections needed.

New anti-VEGF drugs have revolutionized the treatment of wet AMD. One of the drugs – aflibercept – is frequently used as second-line treatment due to its longer lasting effect and slightly different molecular structure compared with older drug, bevacizumab. We

found in our study that aflibercept might provide protection against new-onset visual impairment.

Introduction

AMD is the leading cause of visual impairment in Western countries. It is usually a disorder of elderly people (over 60 years) (Laitinen et al. 2010) and is divided into wet and dry forms. Dry age-related macular degeneration progresses slowly over a period of years to decades. Only seldom does it cause visual impairment ranging from moderate to severe dry AMD. Wet AMD is the more aggressive form of the disorder that, if left untreated, may cause vision to deteriorate rapidly over a few days or weeks. In wet AMD delicate new blood vessels grow under and inside the retina causing leakage, which then leads to edema, hemorrhages and lipid exudation in the sharp vision area called macula. Anti-vascular endothelial growth factor (anti-VEGF) drugs have revolutionized the treatment of wet AMD. They inhibit the growth of neovascular vessels and reduce the fluid in the macula. Nowadays the most frequently used drugs are bevacizumab, ranibizumab and aflibercept. Although these drugs have different mechanisms of action, studies show them to be similar in terms of effect and safety (Tuuminen et al. 2017). Aflibercept is also used as second-line treatment and might improve the treatment. It is used in patients non-respondent to bevacizumab and ranibizumab and also due to its longer-lasting effect.

The etiology of AMD is still not fully understood. Known risk factors like advanced age, tobacco smoking and genetics have been widely studied. Low vitamin intake and unhealthy diet are also risk factors. As a result, a Mediterranean diet and vitamin supplements have been shown to be beneficial in slowing down the progression of AMD. New risk factors like low-grade inflammation are under investigation. Periodontitis, which is an infection of the tissue supporting the teeth, represents one such risk factor.

Cataract or age-related cataract is the leading cause of visual impairment and blindness in developing countries. It is also a disorder of the elderly (Laitinen et al. 2010) and often co-exists with AMD (Bockelbrink et al. 2008). The symptoms of cataract are reduced visual acuity, glare, reduced contrast sensitivity and impaired color vision. The only treatment for cataract is surgery. Today cataract extraction is one of the most common procedures in medicine. Whether cataract surgery worsens wet AMD is much debated. Cataract surgery causes stress on the eye and also on the macula. Pseudophakic cystoid macular edema (PCME) and posterior capsular opacification (PCO) are the most common postoperative complications. However, postoperative topical medication and choice of intraocular lens (IOL) also have an effect on these complications. Low-diopter intraocular lenses are used in long (myopic) eyes and blue-light filtering IOLs as protection against macular disorders. What kind of protection, if any, these lenses provide for the macula is currently under investigation.

Review of the literature

The macula was first described in the literature by an Italian ophthalmologist from Milan, Francesco Buzzi (Belloni 1956) in 1782. At that time it was referred to as the yellow part of the retina, lateral to the optic disc. Macula lutea was first used as a term in the literature by Samuel Thomas von Sommering in 1799 (Schwartz & Leffler 2014). However, age-related macular degeneration was first described in the literature in 1875 by Pagenstecher (Verhoeff & Grossman 1937) and Genth (Pagenstecher H 1875). In 1875 Haab (Bird et al. 1995) described the disciform type of the disease and labeled it senile macular degeneration or senile macular disease (Haab 1885). Drusens, which are one of the hallmarks of dry AMD, were first described by Franciscus Donders in 1855 (Donders 1855) as "Colloidkugeln". A year later Heinrich Müller used the term AMD with drusen (Müller 1856). In 1967 Gass (Gass 1967) gave some insight into the pathophysiologic features of the disorder by showing a link between drusen and wet AMD (Gass 2003). In 1970 (Gass 1970) referred to geographic areas of atrophy (GA) in his first atlas, and in 1976 (Blair 1975) described retinal pigment epithelium (RPE) atrophy in "senile macular degeneration". The disorder was initially referred to as senile macular degeneration, later age-related maculopathy (ARM) or age-related macular degeneration (ARMD). Nowadays AMD is widely accepted and used (Ferris et al. 2013). In 1982 polypoidal choroidal vasculopathy was found as an entity of wet AMD (Yannuzzi 1982).

Treatment of neovascular AMD was first accomplished by direct laser photocoagulation, which became available in 1983. It was effective in only a minority (15%) of wet AMD cases and, because of relapses, permanently benefited only 10% of cases (Moisseiev et al. 1995). In 1999 photodynamic therapy with verteporfin gave new hope for patients. Approximately 33% were suitable for the treatment, which was the first treatment that could be used under the sharp vision area, and 60% of these benefited.

In 2006 came VEGF inhibitors, first pegaptanib (Gragoudas et al. 2004) then ranibizumab (Rosenfeld et al. 2006) and bevacizumab (Martin et al. 2011). Anti-VEGF drugs are nowadays the mainstay of wet AMD treatment. These drugs are injected with a needle into the vitreous cavity. They lower the levels of VEGF in vitreous humor and in the retina and prohibit the growth of a neovascular membrane in the choroid, under the RPE and in the retina. The only problem is that the drugs need to be administered every month or no more than every 16 weeks (Taipale et al. 2020). Four drugs are used today: bevacizumab, ranibizumab, aflibercept and brolucizumab.

Some experimental treatment modalities have also been used, among them low-dose radiation, teletherapy (Chakravarthy et al. 1993) and epimacular brachytherapy (Jackson et al. 2020) but without marked success.

Age-related cataract is the leading cause of blindness in developing nations. WHO estimated in 2010 that it accounted for 51% of blindness in the world, which is approximately 20 million people (Pascolini & Mariotti 2012). Cataract, or crystalline lens, was first mentioned by Rufus, the earliest author of a book on anatomy (Jaffe 1996). Dating back to 800 BC, couching was for a long time the treatment of choice (Asbell et al. 2005). The Indian surgeon Sushruta was mentioned in the literature as operating on a cataract by couching in 600 BC (Grzybowski & Ascaso 2014). In the operation the nucleus was pushed down and backwards with a needle into the vitreous humor. Interestingly, a goat tries to remove a cataract by going to a bramble bush and applying its eye to a thorn in the same way as in couching (Leffler et al. 2018). Intracapsular extraction of a cataract (ICCE) dates back to the mid-18th century and extracapsular cataract extraction to the second half of the 20th century. In 1949 Ridley (Sarwar & Modi 2014) implanted his first intraocular lens. It was widely used in England, but complication rates were high (Ridley 1954). Unfortunately, it was soon abandoned. Quite surprisingly, Casanova (1725-1798) mentioned in his memoirs that he discussed artificial lens implantation after cataract operation with the Italian oculist Tadini. Casanova passed the idea to Dresden court ophthalmologist Casaamata, who tried the procedure around 1795 but without success (Taieb 1955).

Enthusiasm for intraocular lens implantation was still high after Ridley's time and in 1953 Baron implanted the first anterior chamber lens (Baron 1953). Later, surgeons gradually accepted this surgical procedure (although some criticism persisted) and started to implant IOLs using superior knowledge and more advanced equipment. Nowadays phacoemulsification surgery, invented by Kelman in 1967, is the treatment of choice (Pandey et al. 2004). Complication rates were much higher in those days, and one such complication was cystoid macular edema, which was recognized by Gass and Norton in 1968 (Gass & Norton 1969). A decade ago came femto-second laser assisted cataract surgery, which is as good as the old method but is very expensive (Roberts et al. 2020).

1. Definition and classification of age-related macular degeneration

AMD is the leading cause of visual impairment in the Western world (Lim et al. 2012; Mitchell et al. 2018). It is divided into dry and wet, or exudative, forms. The dry form accounts for about 90% of cases and can be subdivided into early, intermediate and late stages.

1.1 Dry AMD

Dry AMD is more common than wet AMD and accounts for 90% of all cases of the disorder. AMD has several classifications. In population studies AMD is classified as either early or late stage. In clinical studies dry AMD is classified using the Age-Related Eye Disease Study (AREDS) scale. Drusens, which are the hallmark of dry AMD, are graded according to their size, type and area. Pigmentary changes are classified as hyperpigmentation, depigmentation and geographic atrophy (Davis et al. 2005). The basic clinical classification (Beckman classification) categorizes AMD as early, intermediate or late according to pigmentary changes and size of drusens (Ferris et al. 2013). Small hard drusens (<63 microns) or druplets in the macula are considered to be due to normal aging, but medium-sized drusens (>63 – < 125 microns) but without pigmentary changes are regarded as early AMD. Large drusens (>125 microns) and extensive medium sized drusens with pigmentary abnormalities are categorized as intermediate AMD (Klein et al. 2014). Neovascular and atrophic entities are labeled late AMD (Mitchell et al. 2018). In dry AMD slow progression leads to RPE, neuroretinal and choriocapillaris apoptosis and central visual loss. Drusens, which are composed of proteins and lipids, are of two types – hard and soft.

Pigment epithelial detachment (PED), geographic atrophy (GA), intraretinal fluid (IF) and subretinal fluid (SRF) are connected with late-stage AMD. PED seen without neovascular membrane is considered to be the dry form. PED can be divided clinically and angiographically into drusenoid, fibrovascular and serous types (Tyagi et al. 2018). Drusenoid PED is formed from a large area of confluent soft drusens (Roquet et al. 2004). PEDs reduce visual acuity only when accompanied by other findings such as intraretinal fluid (Schmidt-Erfurth et al. 2017). GA is late stage dry AMD and usually starts from a small area that gradually enlarges. The rate at which this happens can be predicted and calculated (Fleckenstein et al. 2018). Dry AMD progresses gradually over years or decades

and only seldom causes visual impairment. In 5 years only 5% of early dry AMD cases develop to become late AMD (Lim et al. 2012). Despite this, dry AMD should be monitored regularly (for example, once a year) by an ophthalmologist because of the risk of development into wet AMD. Patients can also test their sharp vision at home by using Amsler's grid, which is a good adjunctive tool but has been reported to have a sensitivity of only 50% (Loewenstein et al. 2003).

1.2 Wet AMD

Wet, exudative or neovascular AMD is the most severe form of the disorder; it progresses rapidly and if left untreated can cause visual impairment. Before effective treatment became available some 50% of patients became severely visually impaired (vision poorer than 0.1 Snellen acuity with best corrected refraction) in 5 years (MPSG 1993). If there is wet AMD in one eye, the risk of developing wet AMD in the other eye within 3-5 years is about 30 - 50% (MPSG 1993; Rasmussen et al. 2013). The risk can be calculated (NEI 2019). The disease itself is located in the area of sharp vision and seldom causes blindness itself but can impair reading vision. Typical findings are intraretinal edema and/or subretinal fluid, PED, superficial intraretinal (Gass et al. 2003), preretinal and/or subretinal hemorrhages and lipid exudations. This is because in wet AMD delicate neovascular vessels grow under the RPE in the choroid. These can penetrate Bruch's membrane (the membrane between pigment epithelium and choroid) and grow under or above the pigment epithelium. Fibrovascular PED is seen in 10% of cases of neovascular AMD (Clemens et al. 2017).

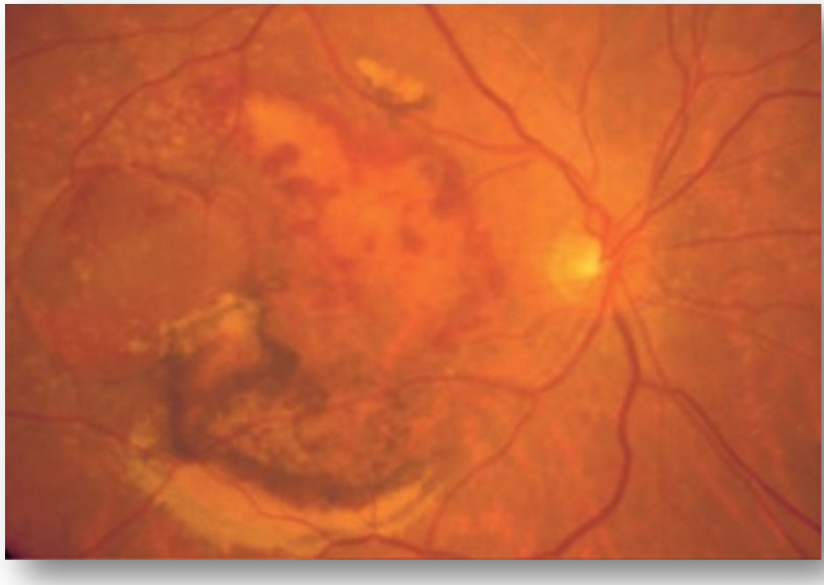


Figure 1. Image of neovascular AMD. Old fibrotic scar, PED, drusens and intraretinal/subretinal hemorrhage. Reprinted from Ophthalmology: Journal of the American Academy Ophthalmology, vol 127, Number 4S, April 2020, Retrospective of Landmark Contributions. Cover photo. Copyright (2020), with permission from Elsevier.

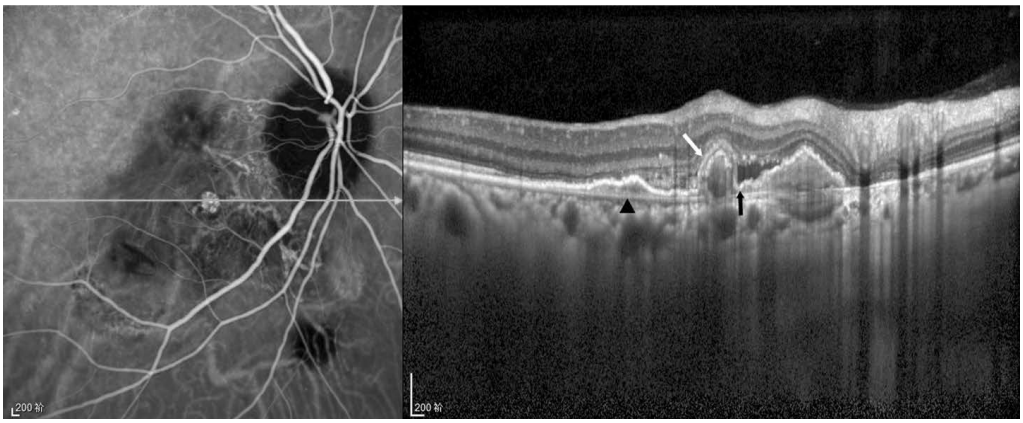
There are three variants of wet AMD: type 1 MNV (macular neovascularization), where the neovascular network is situated under the RPE (occult neovascularization), type 2 MNV, where the membrane is above the RPE (classic neovascularization), and type 3 MNV (retinal angiomatous proliferation) where choroidal neovascularization (CNV) originates from the retina and can communicate with the retinal or choroid circulation (Farecki et al. 2017). The classic lesion is either predominantly or minimally classic. In a minimally classic lesion the neovascular membrane area is less than half of the whole lesion size as seen in fluorescein angiography, while in the predominantly classic lesion it is greater (>50% of total area) (TAP 1999; Seitsonen et al. 2008).

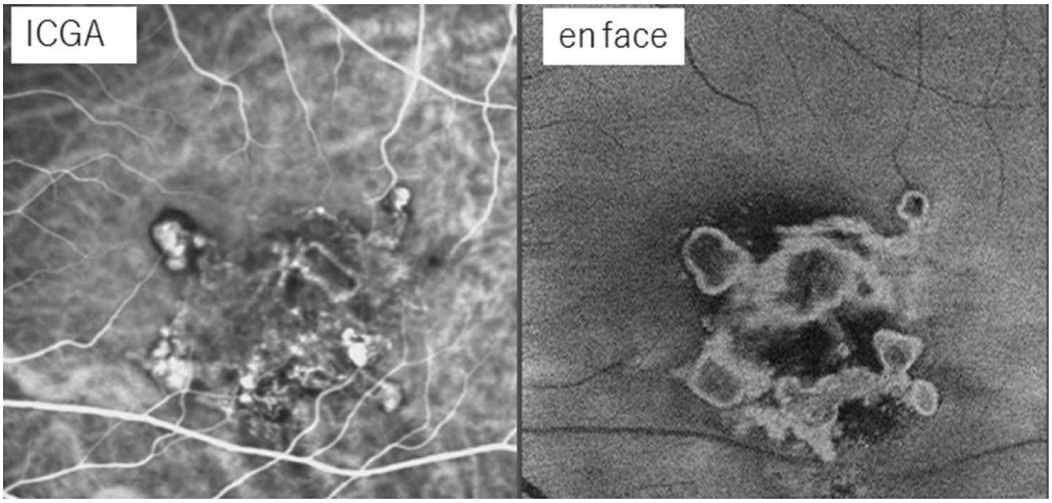
Retinal angiomatous proliferation (RAP) or MNV type 3 (delineated into three stages) is estimated to be involved in 12-15% of newly diagnosed wet AMD cases. It originates from retinal vessels which anastomose with choroidal neovascularization with a “hot spot” (seen in ICG) (Tsai et al. 2017). It is often associated with PED and reticular pseudodrusens (which are small subretinal drusenoid deposits in the macula) (Chang et al. 2016). In stage I there is intraretinal neovascularization, in which neovascularization

progresses toward both anterior and posterior boundaries of the retina. Retinal-retinal anastomosis is seen in 30% of cases. Intraretinal edema and hemorrhages might also be seen. In stage II intraretinal neovascularization extends to subretinal neovascularization past the photoreceptor layer. Neuroepithelial detachment, hemorrhages and intraretinal edema may be seen. Stage II can be subdivided further into those with PED and those without PED. In stage III choroidal neovascularization is associated with vascularized PED and retinal choroidal anastomosis. Choroidal neovascularization can be diagnosed by angiography. In stage III there is retinal-retinal anastomosis in 36% of cases (Tsai et al. 2017). The risk factors for RAP are the same as for wet AMD generally. In one study the incidence of systemic diseases in RAP patients was high. The prevalences of high blood pressure, coronary artery disease and hypercholesterolemia prevalence were 81%, 37% and 19%, respectively (Gross et al. 2005).

Polypoidal choroidal vasculopathy (PCV) is one type of neovascular AMD, and studies have shown that in the European population it is involved in 8-12% of wet AMD cases (Cheung et al. 2018). There exist aneurysmal dilatations, polyps or “grapes” under the RPE, in the choroid, which are visualized more clearly using indocyanine green angiography (ICG). These polyps are weak and delicate and often cause lipid exudation (Cheung et al. 2018). Biomicroscopically these polyp lesions are orange in color. The predilection for PCV is a pigmented fundus, which means that the incidence in persons of African descent is noticeably higher. Nowadays, patients from the Far East and Southeast Asia are also mentioned widely in the literature (Dansingani et al. 2018). The risk factors for PCV are the same as for AMD. In one study, cigarette smoking increased the risk of PCV 4.4 times (Cackett et al. 2011). A high body mass index has been found to be one risk factor (Woo et al. 2015). Some studies report high blood pressure to be a risk factor (Chung et al. 2016).

Peripapillary choroidal neovascularization is located within one-disc diameter of the optic nerve head. It is estimated to involve 10% of all CNV cases (Jutley et al. 2011). It causes visual symptoms only if the neovascular membrane is located near the macula or if hemorrhages/exudates approach towards the fovea.





Figures 2 and 3. Polypoidal choroidal vasculopathy. Polyps in the macula seen in FA, OCT, ICGA and en-face images. Reprinted from Ophthalmology: Journal of the American Academy of Ophthalmology, vol 125(5), Cheung et al, Polypoidal Choroidal Vasculopathy Definition, Pathogenesis, Diagnosis and Management, p. 708-724, Copyright (2018), with permission from Elsevier.

Pachychoroid disease has recently been recognized. It involves PCV, pachychoroid pigment epitheliopathy (PPE), pachychoroid neovasculopathy (PNV) and central serous chorioretinopathy (CSC). All have a thickened choroid in common (Borooah et al. 2020).

One rare subtype or entity of wet AMD is retinal pigment epithelial tear, referred to as an RPE rip. This affects 3-24% of PED patients with wet AMD treated with anti-VEGF therapy. The RPE rip is most commonly seen in vascularized PED, but can also be seen in PCV and RAP lesions, and in some infrequent macular disorders. The RPE rip can be encountered in the natural course of PED, laser photocoagulation, photodynamic therapy with verteporfin and after anti-VEGF therapy. The risk is greater when the PED is higher (Chan et al. 2007; Leitritz et al. 2008; Gelisken et al. 2009; Chan et al. 2010). In one study a PED height ≥ 600 μm was found to substantially increase the risk of RPE rip (Sarraf et al. 2014). However, in a recent real-world study where wet AMD patients were treated with ranibizumab, the incidence of RPE rip was 0.16% (Holz et al. 2020). In high-risk patients (serous vascularized PED), the risk was assessed to be 12 to 17% with anti-VEGF therapy (Clemens et al. 2014). The symptom of an RPE rip is usually a sudden decrease in visual acuity (Ersoz et al. 2017).

1.2.1 Etiology of wet AMD

The cause of wet AMD is unknown, but some risk factors have been identified. Advanced age, smoking and genetic risk factors are the most common strongly associated risks. The effect of smoking might last for up to 20 years after the subject has quit (Zerbib et al. 2014). Moderate associations have been found with high BMI, a history of cardiovascular disease, hypertension and high plasma fibrinogen concentrations (Rim et al. 2017). Diabetes, gender, ethnicity, iris color, cerebrovascular disease and total HDL and triglyceride levels show weak associations (Frank et al. 2000; Chakravarthy et al. 2010). Different results have been reported for the link between obesity and AMD (Zhang et al. 2016; Jaisankar et al. 2018). A low dietary intake of antioxidants is another risk factor (Seddon et al. 2016).

AMD is a multifactorial disorder for which genetic risk factors have been widely studied. Family aggregation and twin studies have shown that the prevalence of AMD is higher in first-degree relatives (23.7%) compared to relative controls (11.6%), with an OR of 2.4. For monozygotic and dizygotic twins the heritability of early and advanced AMD is estimated to be 46% and 71%, respectively (Warwick & Lotery 2018). Genomic region investigations have revealed that chromosomes 1 and 10 were responsible. 52 common and rare variants at 34 genetic loci have been identified as being associated with late AMD (Fritsche et al.

2016). Complement factor H (CFH) and ARMS2 are the major AMD susceptibility genes. Y402 polymorphism has been identified in CFH as a major risk factor for wet AMD.

Inflammation is also thought to be one possible etiological factor (Klein et al. 2008; Bhutto et al. 2016). Helicobacter pylori, Chlamydia pneumoniae and Cytomegalovirus infections have been investigated, but no strong association has been reported (Miller et al. 2004). CRP and serum IL-6 (Seddon et al. 2005; Krogh Nielsen et al. 2019) and aqueous humor cytokines (IL-6, IL-8) are higher in AMD patients than in control patients (Mimura et al. 2019; Subhi et al. 2019). CRP is divided into two independent forms: pentameric (pCRP) and monomeric (mCRP). In a recent study, mCRP was elevated in the choroid and Bruch's membrane in the high-risk CFH genotype (Chirco et al. 2016). The most recent finding is periodontitis, which has been found to have a mild association with wet AMD (Brzozowska & Puchalska-Niedbał 2012; Karesvuo et al. 2013; Wagley et al. 2015; Pockpa et al. 2019; Sun et al. 2019), the latest discovery being an interaction between periodontal pathogen P. gingivalis and RPE cells (Arjunan et al. 2020).

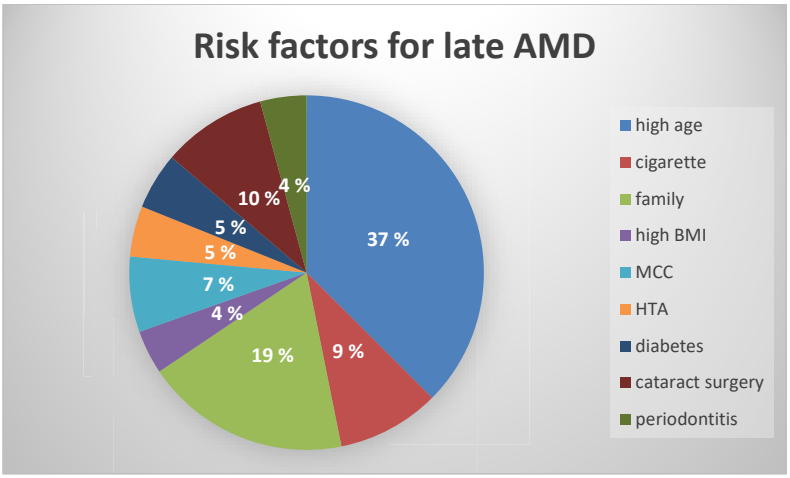


Figure 4. Risk factors for late AMD.

1.2.2. AMD-induced visual impairment

The number of AMD patients worldwide was estimated to be 200 million in 2020, predicted to rise to 300 million by 2040 (Wong et al. 2014). In the People's Republic of China the numbers were 31 million in 2020 and expected to reach 55 million in 2050 (Wu & Sun 2019). AMD affects approximately 4% of the adult population in Finland: 12% of those 65 years or older and 27% of those 85 or older (Laitinen et al. 2010). An earlier study found the prevalence of wet AMD to increase after 70 years of age to 3.7% and to peak at 17% after the age of 85 (Laatikainen & Hirvelä 1995). According to the Finnish Register of Visual Impairment and the Finnish Institute for Health and Welfare, in 2018 AMD was the reason for visual impairment in 41% of the entire population and in 58% of those over 65 (Ojamo 2018). In the UK, AMD is the cause of blindness (Snellen acuity under 0.05) in 58.6% of cases and of partial loss of sight in 57.2% of the population as a whole (Bunce et al. 2010). The incidence of AMD is greater in women than in men, and the risk among white Europeans is twice that for Asians (Mitchell et al. 2018). In the USA the incidences of early and late AMD among white people are 5.3% and 4.1%, among Chinese 4.5% and 2.2%, among Hispanic 3.3% and 0.8%, and among black people 1.6% and 0.4%, respectively. Women, especially whites, are at greater risk of developing AMD (early AMD 6.4% and late AMD 4.0%) than men (early 3.7% and late 1.6%) (Fisher et al. 2016).

PRINCIPAL DIAGNOSES OF VISUAL IMPAIRMENT

Registered visual impairment in Finland in 2019 (N = 18 176)

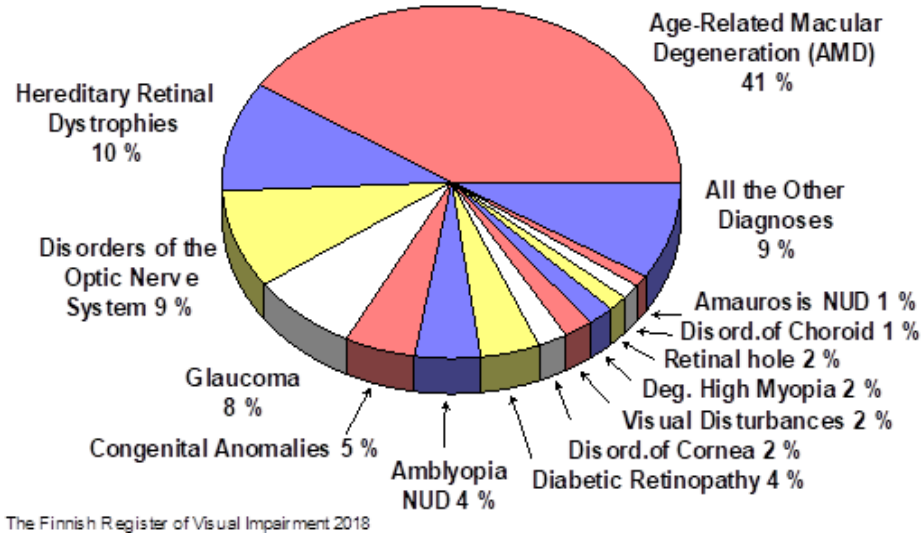


Figure 5. By permission of Matti Ojamo from the Finnish Register of Visual Impairment, Helsinki, Finland.

1.2.3. Symptoms of wet AMD

Early AMD is usually symptomless, but in late-stage AMD the main symptom of newly developed wet AMD is metamorphopsia (which means distortion in the perception of shape and alterations in perceived size (micropsia and macropsia)) when reading, watching TV or driving. This means that straight lines are seen as curves. Vision can sometimes deteriorate rapidly and there can be missing areas in the image or central scotoma, something that has also happened in GA (Leinonen & Hyvärinen 2008). Color vision problems are also encountered. Only very rarely can it cause vision loss due to vitreous hemorrhage, subretinal hemorrhage or RPE tear. End-stage wet AMD results in a fibrous scar and atrophy to the retina, which can cause visual hallucinations called Charles Bonnet syndrome (Niazi et al. 2020). Amsler's grid is a very important tool for assessing dry AMD at home (Yannuzzi 1982) and its possible change to the wet form.

2. Clinical findings and evaluation of wet AMD

2.1 Visual acuity

Visual acuity is the gold standard for testing vision. In 1679 Hooke came up with the idea of the minimal separation between two point sources of light as a measure of vision. Later, in 1863 Professor Hermann Snellen of Utrecht developed his classic test letters. Correct identification of white areas between the black elements of the letter is essential (Duker 2009). In a Snellen test visual acuity is described as the distance over which the test is made divided by the distance at which the letter would subtend 5 minutes of arc vertically. Thus at 6 meters a 6/6 letter subtends 5 minutes of arc, a 6/12 letter subtends 10 minutes and finally a 6/60 letter 50 minutes of arc. A Snellen fraction can also be expressed as a decimal (for example 6/6 = 1.0 and 6/12 = 0.5) (Kanski 2007). However, there are shortcomings in the Snellen method (smaller letters are harder to recognize than bigger ones, and some letters (C, D, O, G) are inherently harder to recognize than others). Base 10 logarithm of the minimum angle of resolution (LogMAR) and Early Treatment Diabetic Retinopathy Study [ETDRS] charts can be used, especially in macular diseases . Visual acuity is normally reduced in wet AMD, but can sometimes be normal. In one study mean visual acuity was 0.4 Snellen units at baseline and increased with treatment after 1 year to 0.6 (Gillies et al. 2019). The reasons for deterioration of vision are intraretinal edema, SRF, exudates or hemorrhages, scar and GA. If visual acuity is under 0.0625 Snellen units treatment is not necessarily started because of low expectations of any benefit. There are however exceptions, such as when only one eye and cataract cause vision to deteriorate. Also, treatment is not started if the risks outweigh the benefits.

2.2 Color fundus photography (CF)

CF is regular light photography and the image is two-dimensional. It can also be used to obtain red-free images. In wet AMD, the image show drusens, pigmentary changes, atrophy, scars, hemorrhage, exudates and edema. Edema, however, is more difficult to detect than it is from three-dimensional images. In one study, CF combined with OCT showed fairly good results in diagnosing wet AMD. Only 2.5% of an entire population had retinal hemorrhage, which was seen only by slit-lamp biomicroscope (Mookhtiar & Downey 2012). When monitoring the disease, retinal hemorrhages are better seen in CF than in OCT or infra-red images (Hibbs et al. 2011)

2.3 Biomicroscopical picture

The slit-lamp biomicroscope was invented in 1911 (Ehinger & Grzybowski 2011; Timoney & Breathnach 2013) and the inventor, Allvar Gullstrand, received the Nobel Prize for Medicine or Physiology. Nowadays the Carl Zeiss® and Haag-Streit® are the leading and most often used slit-lamp instruments. A funduscopic examination with a slit-lamp biomicroscope and a 90 D, 78 D or 60 D double aspheric lens provides a three-dimensional image of the retina. Intraretinal edema, PED, subretinal, intraretinal and/or preretinal hemorrhages and sometimes lipid exudates can be seen. There are often hard and soft drusens, hypo- and hyperpigmentation and geographic atrophy secondary to dry AMD. In the case of vitreous hemorrhage visibility is reduced and it is necessary to use ultrasound.

2.4 Optical coherence tomography (OCT)

Optical coherence tomography is an excellent way to examine the retina and is today used in almost every AMD patient. It was first introduced commercially in 1996 (Fujimoto & Swanson 2016). It visualizes photoreceptor layers, RPE, Bruch's membrane, optic nerve head and choroid. The image obtained depends on how the ray of light (infrared 820nm) is reflected back from the bottom of the eye (as with ultrasound). The information obtained is processed by computer and presented either numerically or graphically. The study is noninvasive and takes about a couple of minutes. The OCT instrument uses an interferometer to quantify these differences in reflectivity and create the signal. OCT can measure very short time intervals and this means that the resolution is very good. Cataract and other medium opacities adversely affect the quality of the images obtained.

A characteristic finding in wet AMD is intraretinal and subretinal edema, indicating that macular thickness has increased. In OCT central subfield macular thickness (CSMT) and foveal and maximal thickness are usually increased. In wet AMD there can be subretinal fluid, in other words neuroepithelial detachment (NED), due to leakage of the neovascular vessels. There can be PED, but this may also apply in the absence of wet AMD. Subretinal hyperreflective material (SHRM) may include an admixture of serum, fibrin and

inflammatory cells (Kumar et al. 2020). Fibrosis is the build-up of collagen deposition tissue. The neovascular membrane can sometimes be seen under the NED.

2.5 En-face imaging

Traditional OCT and advancement in data processing and software has led to the development of en-face OCT which produces by combining OCT data with transverse confocal analysis transverse images of retinal and choroidal layers (Lau et al. 2015). It gives extensive overview of pathological structures with single image. En-face image is useful indicator of visual acuity in geographic atrophy. Also the reticular pseudodrusen, AMD and polypoidal choroidal vasculopathy can be diagnosed with en-face OCT. It is handy because of the lack of dye like there are in FA and ICG. In one pilot study the wet AMD was seen even better on en-face OCT than in conventional imaging (Stopa et al. 2008).

2.6 OCT angiography

OCT-A is the latest achievement in technology to be promoted as an alternative or adjunct to classic fluorescein angiography. OCT-A shows streaming blood and the vascular layers and neovascular membrane in the retina without dye. It lacks side-effects like those associated with FA (vomiting, hypersensitivity reactions and cardiovascular problems). It is less invasive, faster, has higher resolution and depth-resolved imaging modality. FA shows the superficial capillary network, but OCT-A visualizes superficial, deep, choroidal and even middle capillary plexuses. OCT-A allows 3-dimensional analysis of most of the retinal and choroidal layers (Farecki et al. 2017). Different devices are commercially available from Zeiss, Optovue, Heidelberg and Topcon (Munk et al. 2017).

2.7. Autofluorescence imaging

Autofluorescence is a rapid, noninvasive method for assessing RPE health. Autofluorescence is the fluorescence emitted by a tissue after excitation by radiation of a suitable wavelength. Excitation is provided by an SLO blue laser (488nm) and a 500nm barrier-filter is also used to avoid autofluorescence from other ocular structures. Light

reacts with lipofuscin to produce a hyperautofluorescence image. Geographic atrophy can be seen as a hypoautofluorescence area or probable reduced autofluorescence because of missing RPE. The surroundings or the transitional zone between a healthy retina and geographic atrophy area are seen as hyperautofluorescence. In exudative AMD autofluorescence is helpful in detecting serous pigment epithelial detachment (PED) (Tan et al. 2016; Takasago et al. 2019; Battaglia Parodi et al. 2020).

2.8 Fluorescein angiography (FA)

In the 1960s sodium fluorescein injected intravenously provided better visualization of the retinal vasculature (Patel & Kiss 2014). FA contrast agent (sodium fluorescein) is injected into the circulation in order to obtain additional information about the retinal vasculature. Images are taken at different time intervals (seconds to minutes) allowing visualization of choroidal and arterial and venous filling and clearance. A good quality angiogram needs to have adequate pupillary dilatation and clear media. Adverse effects differ from mild (nausea, vomiting, itching) to life threatening (anaphylactic shock). That is why it is beneficial to have an anesthesiologist in attendance (Kanski 2007). The neovascular membrane can be seen in type 1 MNV (classic lesion) (the neovascular membrane appears hyperfluorescent in the early phase of FA). In an occult lesion it is hard to see the membrane. No fluorescence can be seen under the RPE, but background fluorescein can be seen. In type 3 MNV the FA demonstrates intraretinal leakage of fluorescein with potential for cystoid macular edema.

2.9 Indocyanine green (ICG) angiography

The use of indocyanine green was introduced in 1969. ICG is a water-soluble tricarbocyanine dye. It absorbs light waves in the near-infrared range of 790-805nm and has an emission range of 770-880nm with the peak at 835nm. It shows under the pigment epithelium, subretinal fluid, shallow hemorrhage and under the pigment and lipid exudation. It is ideal for detecting and evaluating choroidal abnormalities (Duker 2009). The neovascular membrane can also be seen. It visualizes the choroid well but the retina only poorly. Studies have shown that ICG is better than FA in detecting an occult choroidal neovascular membrane under hemorrhagic wet AMD (Kramer et al. 2000). Polypoidal and occult lesions are especially well visualized using ICG angiography. In ICG angiography the choroidal neovascularization is seen as hyperfluorescence. It can be used

in combination with FA. ICG angiography offers a good opportunity to perform "hot spot" laser treatment. It is focal CNV, which is most often either an area of occult CNV or an RAP lesion (Duker 2009). ICG gives an opportunity to treat the feeder vessel. Unlike FA, ICG angiography makes it possible to see under the serous PED (Regillo 1999). Adverse effects occur rarely (0.34%) and are usually mild (nausea, exanthema, urticaria and urgency to defecate). Hypotension requiring treatment for shock is seen only rarely (Obana et al. 1994).

2.10 Microperimetry

Microprimetry provides a way of measuring the visual field of the macular area. It is a psychophysical test that reflects functional vision. Fundus-tracking control makes it possible to overcome fixation losses and eye movements. Commercially available microperimeters include the MP-1 (Nidek, Gamagori, Japan) and the Macular Integrity Assessment (MAIA, CenterVue, Padova, Italy) instruments. Microperimetry cannot detect very small scotoma, particularly when retinal fixation is unstable. In wet AMD, microperimetry shows relative scotoma, depending on the location of atrophy, edema or even hemorrhage of the macula. The sensitivity of the macula can be reduced due to macular thickening, intraretinal edema, fluid or neuroepithelial or pigment epithelial detachment (Midena & Pilotto 2017). Advanced AMD status, older age and reduced retinal thickness were associated with decreased retinal sensitivity (Roh et al. 2019). After anti-VEGF treatment an increase in retinal sensitivity is observed (Hartmann et al. 2015).

2.11 Visual evoked potential (VEP)

Visual evoked potential measures the visual impulse from the eye to the visual cortex. The visual system is irritated by visual patterns and the electrical visual potentials are measured. It is well established that VEP values have connections with macular diseases (Marcus et al. 1983). VEP values improve after treatment of wet AMD (Vottonen et al. 2015), but the usefulness of VEP in the treatment and follow-up of wet AMD is debated .

2.12 Color vision

The color vision test examines the ability of an observer to discriminate the distribution of different wavelengths. A defect is described in terms of abnormalities in color matching, color discrimination, color arrangement and spectral sensitivity. Color matching is tested with an anomaloscope, whereas color discrimination is tested with the commercially available Farnsworth-Munsell 100 hue test. However, in clinical practice the Farnsworth D-15 is quicker and easier to use. Color vision changes in AMD are a subject of research. In early AMD the yellow-blue (tritan) color defects are generally recognized and these tend to worsen in late-stage AMD (Neelam et al. 2009).

3. Differential diagnostics of wet AMD

Some common, and also rare, diseases mimic wet AMD. Central retinal venous occlusion (CRVO) and branch retinal venous occlusion (BRVO) have the same symptoms, but the clinical picture is different. In BRVO and CRVO microinfarcts, flame-shaped hemorrhages, venous tortuosity and edema dominate the retinal picture. Retinal macroaneurysm is dilatation of the retinal artery and might, on rupturing, cause subretinal hemorrhage that could mimic wet AMD. Sometimes massive subretinal hemorrhages might resemble a tumor-like choroidal melanoma or cavernous hemangioma (Pitkänen et al. 2014). Pachychoroid pigment epitheliopathy (PPE) resembles AMD, but without subretinal fluid or neovascular membrane, and patients are younger (Borooah et al. 2020). Pachychoroid neovasculopathy (PNV) is very similar to wet AMD, but is characterized as changes without drusens, by its earlier onset, thicker choroid and higher prevalence of RPE abnormalities (Pang & Freund 2014). Pathologic myopia (>6 diopters) affects people of working age and, like AMD, causes CNV and can also cause rapid vision loss (Cheung et al. 2017). Cystic macular edema (CME) acts similarly to wet AMD, which is a complication in cataract and glaucoma surgery. Central serous chorioretinopathy (CSC) has the same symptoms and also the same kind of clinical picture, neuroepithelial detachment, but without drusens. It is usually a disease of younger males. Macular hole and macular pucker or epiretinal membrane (ERM) also affect the macula causing central scotoma in the hole and blurred vision and metamorphopsia in the pucker. The prevalence of macular holes is approximately 3.3 per thousand in people over 55. The famous American ophthalmologist JD Gass put forward

a new hypothesis in 1988 that an idiopathic macular hole is created by the tangential forces of vitreous remnants acting towards the macula (Gass 1988). OCT differentiates this disease from AMD (Agarwal 2012). Vitreomacular traction syndrome (Errera et al. 2018) is a rare entity as are macular teleangiectasia type 1 (Lee Kim et al. 2017) and type 2 (Charbel Issa et al. 2013). Diabetic maculopathy and macular edema (DME) are located in the central part of the retina, in the macula, and are sometimes very hard to differentiate from wet AMD. There can be small intraretinal hemorrhages, edema and lipid exudates as in wet AMD. FA helps in making the diagnosis. In FA the dye leaks into the subtle neovascular membrane and can be seen for example in type 2 MNV as late leakage and as a well-defined area. It is rarely mentioned that AMD should be distinguished from dominantly inherited progressive juvenile foveal dystrophy associated with drusen-like changes and macular staphyloma, basal laminar drusens and macular degeneration and pattern dystrophy (Agarwal 2012).

4. Treatment and follow-up of wet AMD

4.1 Prevention

The progression of wet AMD can be postponed from intermediate stage AMD to late AMD. Previously, high-dose zinc and antioxidant (beta-carotene, vitamins C and E) supplements (AREDS formula) were used. However, there were side-effects and beta-carotene was replaced by lutein and zeaxanthin (AREDS and AREDS2 studies) (Seddon et al. 2016). The odds are lowered significantly in the case of intermediate AMD or late AMD in the other eye, so that it is recommended to take these supplements (Chew et al. 2013): reduction rates have been reported in at least moderate visual acuity loss in an antioxidant + zinc group, 0.73 OR, 99% CI, 0.54-0.99 (AREDS 2001). The Mediterranean diet (rich in vegetables, fruits, legumes and fish) has been proved to reduce the risk of developing wet AMD by 41% (Merle et al. 2019). Both the AREDS and AREDS2 studies produced the same results (Keenan et al. 2020). Giving up smoking or cutting down the number of cigarettes per day helps prevent the progression of wet AMD (Rim et al. 2017). To lower the risk it is also important to lose weight (in obese persons), and to treat hypertension and cholesterol levels (Chakravarthy et al. 2010).

4.2 Anti-VEGF injections

VEGF is a Y-shaped molecule derived from vascular endothelium that accelerates the growth of delicate neovascular vessels. VEGF levels can be measured from vitreous humor by enzyme-linked immunosorbent assay (ELISA) (Hsu et al. 2016). The VEGF family has five members in mammals: VEGF-A, VEGF-B, VEGF-C, VEGF-D and placental growth factor (PIGF). In ophthalmic use these anti-VEGF drugs bind to VEGF-A, VEGF-B and PIGF. VEGF-A is a key regulator of developmental, physiological and pathological neovascularization. It is divided further into nine isoforms, the most abundant being $VEGF^{165}$. VEGF interacts with receptors VEGF-R1, R2 and R3 so that VEGF-A interacts with R1 and R2 and VEGF-C and D with R3. Interaction activates receptor dimerization and the cascade of downstreaming signaling transduction pathway, which leads to increased vascular permeability, endothelial cell activation, proliferation, invasion and migration (Ciombor et al. 2013). VEGF-R1 transmits different vascular development and growth signals. VEGF-R2 is mainly responsible for VEGF signaling in angiogenesis and VEGF-R3 for lymphangiogenesis (Tammela et al. 2008).

In 2006 came VEGF (vascular endothelium growth factor) inhibitors, which are nowadays the cornerstone in the treatment of wet AMD. Anti-VEGF is a molecule that inhibits the activity of VEGF, a critical mediator of physiological angiogenesis and pathological angiogenesis (Ferrara et al. 2003). Anti-VEGF drugs are injected into the eye with a needle. Besides lowering levels of VEGF in vitreous humor, anti-VEGF agents also reduce levels of VEGF in serum (Wang et al. 2014). In addition to wet AMD, the injections are used in CRVO, DME, corneal neovascularization and retinopathy of prematurity (ROP), among others.

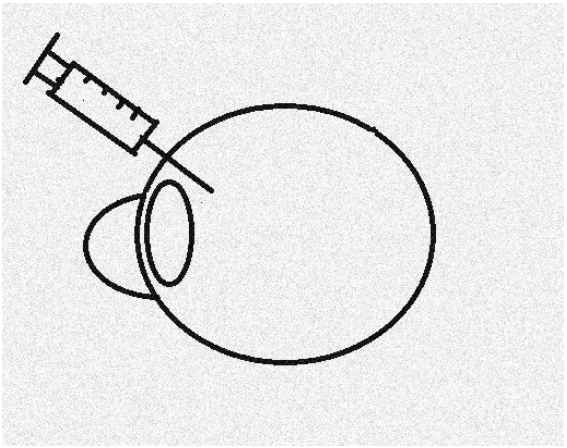


Figure 6. Intravitreal injection.

Anti-VEGF lowers the levels of VEGF in vitreous humor and prevents the growth of neovascular membrane in the choroid and retina. The one challenge is that it should be administered intravitreously every month or in some cases less often, because of its short duration of action. Four drugs are used, namely bevacizumab, ranibizumab, aflibercept and brolucizumab. In recent studies bevacizumab and aflibercept have been found to be equally effective, safe and well tolerated (Tuuminen et al. 2017). The advantage of aflibercept is that it binds to VEGF-A, VEGF-B, PIGF-1 and PIGF-2 molecules, while bevacizumab binds only to VEGF-A. These drugs have greatly improved the visual handicap and deterioration of vision and also visual impairment resulting from wet AMD treatment (Karesvuo et al. 2020). The problem with these drugs is that treatment usually lasts many years. The LUCAS study showed that 62% of patients benefited from the treatment (visual gain >5 letters), 26% derived intermediate benefit (<4 letters) while the remaining patients (9%) did not benefit (decrease > 5 letters) in a 1-year follow-up (Berg et al. 2015). In a 10-year real-world study the mean visual loss from baseline with anti-VEGF therapy was 5 ETDRS letters. The most important prognostic factor was the baseline BCVA and the decline of BCVA was thought to be caused mainly by atrophy (Brynskov et al. 2020). The mild complications of injections are corneal erosion, sugillation, intraocular inflammation, and mild discomfort. The severe adverse effects are vitreous hemorrhage, retinal detachment, endophthalmitis, traumatic cataract, elevated intraocular pressure and central artery occlusion. Systemic complications, like a thromboembolic event, heart attack or stroke were the same as in the placebo group (Rosenfeld et al. 2006; Heier et al. 2012; Moja et al. 2014). In Finland a total of around

90,000 anti-VEGF injections were given in 2017, and the figure is increasing as the "baby boom" generation gets older (Karesvuo et al. 2020).

4.2.1 Pro re nata (PRN)

Pro re nata means that anti-VEGF injections are given as needed depending on the status of the macula. First it is usual to give a loading dose, which means 3 monthly injections, following which the status of the macula is assessed every 4-8 weeks (depending on the drug). Treatment can also be provided without a loading dose. According to the CATT and PRONTO studies retreatment indications are loss of 5 ETDRS letters, hemorrhage in the macula, fluid on OCT, dye leakage or increased size of the neovascular membrane in FA (Lalwani et al. 2009; Martin et al. 2011). The injections are then given every month only if there is activation of the disease (Kvannli & Krohn 2017). PRN is considered as a "reactive" regime. Its pitfall is the yo-yo effect of fluid accumulation which damages the retina (Augsburger et al. 2019). PRN is used globally due to its lower costs and fewer visits compared to monthly visits (Hernandez et al. 2018).

4.2.2 Treat and extend (TER)

The TER regimen means that injections are first given every month, after which treatment intervals and visits are gradually extended, for example by two weeks if there are no signs of active disease on OCT and biomicroscopic fundus examination. The maximum interval is usually up to 16 weeks (Taipale et al. 2020). If there is recurrent disease, fluid on OCT, hemorrhage on fundus examination, or if the neovascular membrane size is increased on FA, the interval is shortened, for example by 2 weeks. A decrease in best corrected visual acuity is not considered a recurrence (Berg et al. 2015). This treatment regimen is considered as "pro-active" which means that injections are given on every visit and the duration is decided at the visit. A Swiss study showed that the TER protocol is able to achieve more visual gain with fewer injections compared to the PRN protocol (Augsburger et al. 2019).

4.2.3 FIX

Injections are given at regular, predetermined intervals, every 4-6 weeks in the case of bevacizumab and ranibizumab, and after 3 loading doses with aflibercept (every 4 weeks) then every 8 weeks (Providência et al. 2018). Treatment is continued until the discontinuation criteria are fulfilled (VA permanently below 0.0625 ETDRS, patient's wishes, risks and adverse effects exceed the benefits) (Tuuminen et al. 2017). Follow-up visits are after every three injections.

4.2.4. Fixed treat and extend (FIXED TER)

The injections are given every month for 3 months, then three times at 6-week intervals and then twice with an interval of 8 weeks. This is followed by one injection after 10 weeks, one injection after 12 weeks, one injection after 14 weeks and then one final injection after 16 weeks. The interval is shortened if there is activation of the disease (fluid in OCT or hemorrhage in the macula), for example from 12 weeks to 10 weeks, etc. (Karesvuo 2021).

4.3. Photodynamic therapy with verteporfin

In 1999 PDT with verteporfin gave new hope to the AMD patient (TAP 1999) and to patients with other disorders, including choroidal hemangioma and central serous chorioretinopathy. Approximately 21% of AMD patients (Haddad et al. 2002) were suitable for the treatment, which was the first that could be given under the sharp vision area, and 60% benefited. The problem with PDT was its high price, but studies have pointed out its cost-effectiveness if the treatment is started early enough and vision loss is initially only moderate (Hopley et al. 2004). In standard protocol PDT, the photosensitive drug verteporfin (6mg/m^2) is injected intravenously, and after 10 minutes low energy laser light (693nm) is directed (laser fluence (50J/cm^2) at the area to be treated to activate the verteporfin. Wet AMD is diagnosed with FA and the area treated is assessed from dye leakage (type 1 and type 2 MNV) (TAP 1999; Lim et al. 2020). The mechanism behind PDT is thought to be that verteporfin accumulates in abnormal choroidal neovascular endothelial cells in increased LDL receptors and causes occlusion when activated by laser. The safety profile is quite good, with visual disturbances (10-15%), photosensitivity

reactions (3%) and back pain (2%) being encountered during treatment (Newman 2016). Acute choroidal ischemia is seen in 1.8% of patients treated with PDT (Isola et al. 2006). After treatment patients are advised to avoid sunlight for 48 h and to wear a wide-brimmed hat and use full skin coverage and sunglasses for 3-5 days, because of skin photosensitivity. To enhance the safety profile, half-dose PDT is used in CSC with and without reduced fluence.

PDT and anti-VEGF therapy can be used together, and some studies have shown the result is greater visual gain with fewer injections and better chances of complete polypoidal lesion regression (Lim et al. 2020).

4.4. Laser photocoagulation

Laser light is made from coherent waves, which means that every light wave is of the same length and oscillates in the same direction and at the same frequency. The first laser was built more than 50 years ago and its use in ophthalmology soon followed. In 1961 it was used with a ruby laser to make ocular lesions (Zaret et al. 1961). The argon laser was introduced in 1964 and was first used with a slit lamp microscope in 1970 (Little et al. 1970). In the 1980s the laser was adopted for use in wet AMD but was effective in only a small number (15%) of wet AMD cases and, because of relapses, permanently benefited only 10% of cases (Moisseiev et al. 1995). In laser treatment the laser induces a direct laser burn, which occludes leaking neovascular vessels. The problem is that it can cause a scotoma in the treated area, which explains why it cannot be used in the sharp vision area. An argon laser (532nm) is also used for polypoidal choroidal vasculopathy, but can cause other unfavorable side-effects like RPE rupture (Gass 1984), and subretinal and vitreous hemorrhages (Gomi & Tano 2008). The krypton red laser (670nm) is used to treat neovascular lesions and especially choroidal lesions like PCV (MPSG 1990). Some patients have benefited from ICG angiography-guided laser photocoagulation and also from feeding vessel photocoagulation (Brancato et al. 2000). Nowadays, lasers are seldom used because of the availability of new treatment modalities.

4.5. Surgical treatment

Surgical treatment is indicated for hemorrhagic cases and also in very rare cases if there is blood subretinally in the macula and especially in the fovea. Pars plana vitrectomy

combined with recombinant tissue plasminogen activator (r-tPA) has been reported to be effective (Boiché et al. 2019). Direct subretinal surgery is performed for the evacuation of submacular hemorrhage and the use of r-tPA is involved subretinally or intravitreously and intraoperatively for clot liquefaction.

4.6 Low vision aid

In Finland ophthalmologists fill out a form for visually impaired people and send it to the Finnish Federation of the Visually Impaired, the Finnish Register of Visual Impairment, and the Finnish Institute for Health and Welfare. These organizations provide help for visually impaired people (vision permanently with refraction correction under 0.3 (Snellen acuity) or whose visual field meets the criteria). Reading aids, social benefits, rehabilitation, psychologist consultations, IT skills, braille, audiobooks, white canes and guide dogs are some examples (NKL). Finland also offers courses for visually impaired elderly people and for those of working age. They can be accommodated during their stay at the Iiris building in Helsinki which is located at the Finnish Federation of the Visually Impaired. Advice on education and studies is also provided. Peer support and culture and spare time support are other important factors (NKL).

5. Periodontitis

5.1 Definition

Periodontitis is an infection of the tissue supporting the teeth. Both Gram- negative and Gram-positive bacteria are involved, though mainly Gram negative. The main bacteria are Porphyromenas gingivalis (P. gingivalis), Prevotella intermedia, Tannerella forsythia, Campylobacter rectus, Treponema denticola, and Aggregatibacter actinomycetemcomitans. In the Finnish Health 2000 survey, 64% of the adult population had periodontitis and 21% had its severe form (Suominen-Taipale L 2008). Severe periodontitis is often compared to acute skin infection, and is approximately the size of a hand in area. Periodontitis causes endotoxemia via inflamed tissue supporting the teeth. Oral and circulating aMMP-8 are elevated (Fritsche et al. 2016). Acute phase protein, for example C-reactive protein (CRP), is elevated and there are elevated concentrations of lipopolysaccharides (LPS), IL-6, IL-8 and TNF-α in the circulation (Cardoso et al. 2018)

compared with people without periodontitis. These are signs of low-grade inflammation in the body.

Systemic diseases have been linked with periodontitis, including Alzheimer's disease (Sochocka et al. 2017), coronary artery disease (Tonetti & Van Dyke 2013), rheumatoid arthritis (de Molon et al. 2019), obesity (Altay et al. 2013), respiratory diseases (Gomes-Filho et al. 2020), oral, lung and pancreatic cancers (Michaud et al. 2017) and osteoporosis (Wang & McCauley 2016). Interestingly, preterm birth and low birth weight have also been linked with periodontitis (Puertas et al. 2018).

5.2. Signs and symptoms

Typical findings are deepened (>4mm) periodontal pockets, calculus and alveolar bone loss. Smokers may have milder symptoms, while in difficult cases discharge from the periodontal pocket might sometimes be one clinical finding. Deepening of the periodontal pockets and alveolar bone loss can cause teeth to become loose. Radiological examination, especially an orthopantomogram (OPG), reveals alveolar bone loss and furcation lesions (which are bone loss at the branching point of a tooth root) (Tonetti et al. 2018).

Periodontitis progresses often without any symptoms. If there are symptoms, they could be gum bleeding on probing (BOP) and swelling and inflammation of the periodontal tissue. The gums might be purple. There may sometimes be detachment or movement of teeth. Bad breath can be one symptom in both gingivitis and periodontitis (Tonetti et al. 2018).

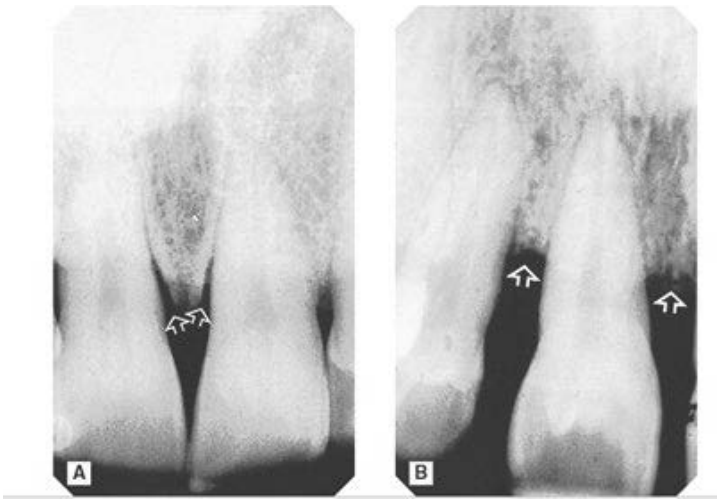


Figure 7. Maxillary incisors: Periapical radiographs show the typical radiographic features of alveolar bone loss in periodontitis. A: Moderate bone loss. B: Severe bone loss. Figure published in Essentials of Dental Radiography and Radiology, 2013, Whaites Eric, Drage Nicholas, Chapter 22, page 286, Fig. 22.5. Permission granted by Elsevier.

5.3. Differential diagnostics

In gingivitis plaque on the surface of the tooth attracts large numbers of white blood cells to the area and this can cause bleeding. Gingivitis is less serious than periodontitis and can be treated by brushing. It is important to differentiate acute periodontal lesions from periodontitis (Herrera et al. 2014). Periodontal abscesses and necrotizing periodontal disease are some examples of acute lesions. A periodontal abscess is often caused by a foreign body and is treated by tooth extraction, drainage, debridement, systemic or local antimicrobials and surgery, depending on the situation. The typical symptoms are pain, tenderness and discharge. Signs are redness and swelling of the gingiva, tooth mobility, tooth elevation and sensitivity to tooth palpation (Ahl et al. 1986). A chronic abscess is usually symptomless or may involve mild symptoms. Necrotizing periodontal diseases are subdivided into three categories: necrotizing gingivitis, necrotizing periodontitis and necrotizing stomatitis (Herrera et al. 2014). Necrotizing gingivitis is characterized by gingival ulcers and necrosis. The symptoms are pain and bleeding. The same symptoms are seen in necrotizing periodontitis. The difference is that in necrotizing periodontitis the necrosis has penetrated to the periodontal ligament and alveolar bone, which might cause the loosening of teeth.

Peri-implantitis is inflammation of the mucosa around a tooth implant and could cause alveolar bone resorption. It is usually preceded by perimucositis as with gingivitis and periodontitis. Clinical findings are redness and edema in perimucositis and bleeding, discharge and implant mobility; on the other hand, peri-implantitis may produce no symptoms. The condition is diagnosed by probing and by radiography (Schwarz et al. 2018).

Pericoronitis is inflammation of the soft tissue of the teeth and usually affects the third molars when they are erupting. It can be both acute and chronic. It is typically present in the mandibular region and is the main cause of tooth extraction in recurring cases. There may also be trismus. (Galvão et al. 2019).

Caries cannot be confused with periodontitis because it affects the tooth itself and can cause pain. Juvenile periodontitis is uncommon and more aggressive during puberty.

5.4. Treatment

Treatment is individually targeted. Primary treatment of gingivitis is essential to prevent periodontitis and is achieved by brushing the teeth twice a day. It is also important to clean the interdental spaces daily using an interdental brush, dental floss, or a dental pick. An electric toothbrush has been shown to be more effective than a manual one (Ikawa et al. 2021). Giving up smoking is essential. Anti-infective treatment by removing calculus by scaling and root planning is performed by a dental hygienist or dentist. Antibiotics are used only in difficult cases, with amoxicillin and metronidazole the golden standard. Surgery may be needed in severe cases (Deas et al. 2016).

6. Age-related cataract and surgery

Age-related cataract, later referred to simply as cataract, is one of the leading causes of visual impairment in developing countries (Flaxman et al. 2017). It causes blindness in 65.2 million people annually (WHO 2019). In the Western world cataract surgery is the most common surgical procedure and one that greatly improves the patient's vision (Kennedy et al. 1985). Diagnosis of both cataract and AMD is easier than for many other eye disorders, for example eye manifestations of immunological diseases (Karma 1986). It has been estimated that in Finland 50 – 60,000 cataract operations are performed annually (Falck et al. 2012).

The symptoms of cataract are gradual worsening of vision, glare, changes in refraction, diplopia, impaired contrast sensitivity and changes in color vision. The criteria for surgery in public health care are quite strict in Finland, when vision in the better eye is worse than 0.5 Snellen acuity, which means that people are about to lose their driving license. The second eye is operated on if the better eye's visual acuity is above 0.5 and when visual acuity is under 0.3 in the worse eye. Exceptions are >2 D anisometropia after first cataract surgery (means that the eyes have unequal refractive power), and subcapsular cataract affecting daily survival, for example in traffic. Surgery is also performed when a cataract is making it harder to monitor underlying diseases like glaucoma, diabetic retinopathy and age-related macular degeneration (Cataracts 2019).

Cataracts are divided into the basic subtypes nuclear cataract, cortical cataract and subcapsular posterior cataract. A hypermature cataract is diagnosed when the lens has become opaque and thus white. A nuclear cataract is usually green and yellow in color, but in advanced cases it can be red and brown depending on the hardness of the lens. The nucleus of the cataract is the core of the lens, which gets harder as the cataract progresses. Cortical cataracts are found near the margin of the lens, with spikes pointing toward the center of the lens. A posterior subcapsular cataract drastically reduces vision and is located at the back of the lens, anterior to the posterior capsule (Mandelblum et al. 2020).

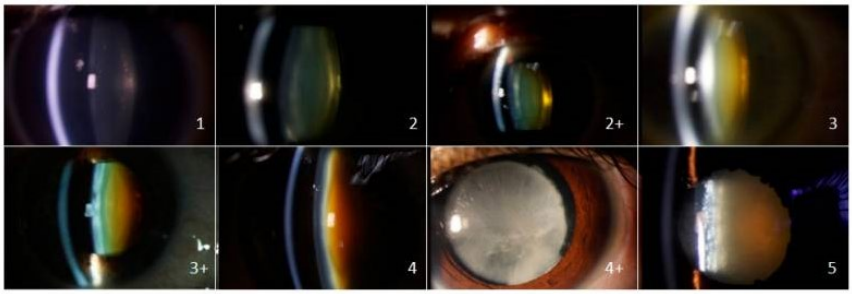


Figure 8. Standard Pre-Operative Nuclear Classification System (SPONCS). Canon EOS slit-lamp photographic examples. From the article: A Simple Pre-Operative Nuclear Classification Score (SPONCS) for Grading Cataract Hardness in Clinical Studies. J Clin Med. 2020. Mandelblum et al. Permission granted by author Dr. Oriel Spierer.

Surgery is usually performed under topical anesthesia as a day procedure. Sometimes surgery is carried out under peri- and retrobulbar anesthesia depending on the patient's status. Surgery is normally completed using ultrasound with a phacoemulsification phaco machine. Nowadays it is also possible to perform the operation by means of femtosecond

laser-assisted cataract surgery (FLACS), although this technique only seems to be as good as the old one and possibly less cost-effective (Walland 2017).

In surgery the surgeon first makes an incision (paracentesis) at the so-called side-port (at 9 o'clock) with a 24-gauge, 15-degree lancet tip blade. The main incision (1.8-3.0 mm) is made with a keratome blade to clear the cornea for the main instruments followed by viscoelastic gel to deepen the anterior chamber. The surgeon then uses continuous curvilinear capsulorhexis (CCC) to remove the anterior lens capsule with a cystotome or rhexis forceps. The next step is hydrodissection, which means separation of the cortex from the capsular bag with balanced salt solution (BSS). The surgeon then divides and breaks the crystalline lens using a phaco machine. There are different techniques for doing this depending on the hardness of the nucleus. Soft nuclei are removed using the "chip and flip" technique, harder nuclei using the "divide and conquer" technique, while the hardest nuclei are usually removed by means of the "stop and chop" technique. Aspiration of the nucleus and cortex fragments are the next stage followed by cleaning of the capsular bag. On completion the surgeon inserts an intraocular lens (IOL) using an IOL injector through the incision and removes the viscoelastic gel. An intracameral antibiotic is then administered. Finally, the incisions are sealed by hydrating the stroma with BSS (Larry 2007).

Complication rates have decreased since the old procedures, ICCE and ECCE methods thanks to the less stressful modern phacoemulsification surgery, while the visual outcomes are also better (Riaz et al. 2006).

Intraoperative complications can occur but are quite uncommon nowadays. Posterior capsular rupture is one complication, others being phaco-burn and breakage of the IOL. Vitreous loss and drop of the nucleus to the vitreous body may occur, especially in difficult cases such as mature cataract operations. In a recent study (Aaronson et al. 2020) senior surgeons experienced a complication rate of 0.36% at the start of the study period compared with 7.03% for residents. At the end of the study period (after 100 surgeries) the rates were 0.32% and 1.32%, respectively.

Postoperative complications are seen more frequently. Mild iritis, pseudophakic cystoid macular edema (PCME), also known as Irvine-Gass syndrome, posterior capsular opacification (PCO) and very rarely endophthalmitis have been reported. PCME is often self-limiting (Aaronson et al. 2020). Very rarely encountered is cornea decompensation (eventually leading to bullous keratopathy), which in some cases might even need partial corneal transplantation.

Nowadays there are many IOL options for patients. Blue-light filtering IOLs ((AcrySof Natural (Alcon), OptiBlue (AMO), AF-1 (Hoya) and PC 440Y Orange Series (Ophtec)) are used because earlier animal and cell culture studies showed that blue light (short wavelength) is harmful to the retina (Downie et al. 2018). One recent study concluded that blue-light filtering IOLs have the same effect as non-blue-light filtering IOLs on the development and progression of wet AMD (Achiron et al. 2020). Blue-light filtering IOLs contain yellow chromophores, which attenuate about half of blue light. These IOLs do not affect color vision or retinal nerve fiber layer (RNFL) fundus photographs (Vuori & Mäntyjärvi 2006). Toric IOLs are used in patients with astigmatism while aspheric IOLs are used to correct spherical aberration. Bifocal, trifocal and multifocal IOLs provide both near and far vision. Astigmatism and myopia can be corrected with toric iris-claw lenses, with which even contrast sensitivity has been found to improve (Dick et al. 2004). IOL diopter power normally varies from mild negative (-6) (Zaldivar et al. 2000; Haigis 2009) to as high as + 34 diopter (Alfonso et al. 2019). Different formulas are used to calculate IOL power (Gökce et al. 2017; Rong et al. 2019) to ensure correct refraction postoperatively.

After cataract extraction, various postoperative eyedrops are used in hospitals. NSAID, steroids and antibiotics are drugs of choice. Prednisolone acetate, nepafenac, diclofenac and levofloxacin are usually used in Finland (Loukovaara et al. 2019). Nepafenac and diclofenac have been found to have the same effect (Ylinen et al. 2018). Steroids have been shown to prevent PCO formation better than NSAID drops (Hecht et al. 2020).

Previous studies have shown that cataract surgery may (Klein et al. 1998; Klein et al. 2002; Cugati et al. 2006) or may not (Armbrecht et al. 2003; Baatz et al. 2008; Dong et al. 2009) increase the progression of wet AMD. In Finland cataract surgery for wet AMD patients is usually performed between injections so that the wet AMD status is as dry as possible (Cataracts 2019).

7. Aims of the study

7.1. Study I

Inflammation has been suggested to be one of the risk factors for wet AMD, and we wanted to study periodontitis and its association with wet AMD.

7.2 Study II

We wanted to study the correlation between anti-VEGF injections with aflibercept as second-line treatment and visual impairment in wet AMD patients in Finland.

7.3 Study III

We studied topical anti-inflammatory medication after cataract surgery and its impact on posterior capsular opacification postoperatively.

7.4 Study IV

Our aim was to study the effect of cataract surgery on wet AMD patients and on wet AMD progression.

7.5 Study V

Our aim was to study cataract surgery and IOL diopter and the rate of PCO.

7.6 Study VI

We studied the effects of blue-light filtering IOLs and non-blue-light filtering IOLs on wet AMD, and whether they have different effects on prognosis.

8. Methods

Data for study I was obtained from the Finnish Health 2000 study. Study I was cross-sectional retrospective in design. General health information (including self-reported diagnosis of AMD) was gathered by questionnaire. Oral health was examined by dentists and x-ray images were taken of alveolar bone, and oral saliva bacteria levels were measured from periodontal pockets. 54 AMD patients were compared with 1,697 non-AMD patients. Pearson's X^2 and analysis of variance tests were used together with logistic regression analysis.

In study II we gathered information from different Finnish hospital and university hospital districts on the use of anti-VEGF drugs (bevacizumab, ranibizumab and aflibercept) during 2015-2017. In five university hospitals and 14 central hospitals the total number of anti-VEGF injections was 232,568. We also obtained data on new cases of visual impairment from the Finnish Federation of the Visually Impaired and the Finnish Institute for Health and Welfare comprising together 1,172 visual impairments.

Study III involved a retrospective registry-based analysis of 25,818 patients who had undergone cataract surgery between 2014 and 2018 at Helsinki University Hospital in Finland. A total of 13,368 patients were included in the analysis. Nd:YAG capsulotomy was considered as PCO and rates of PCO in postoperative steroid and NSAID treatments and their combination were compared. Kaplan-Meier and Cox regression analyses were used.

In study IV we investigated the effect of cataract surgery on wet AMD. This was a retrospective registry-based study. Data was obtained from Helsinki University Hospital patients' healthcare registry. A total of 111 eyes that had undergone cataract surgery during 2014-2018 were included. The treatment protocol was fixed TER with wet AMD treatment. Visual acuity and central subfield macular thickness (CSMT) were recorded at the time of wet AMD diagnosis, before surgery, postoperatively and 1 year after surgery.

Study V was a cohort study in which we compared PCO rates in different IOL diopter study groups. A total of 14,264 cases were examined at Kymenlaakso Central Hospital during the study period of 2014-2018.

In study VI we compared BLF IOLs and non-BLF IOLs in terms of the overall risk of developing wet AMD. The patients were from Kymenlaakso Central Hospital in Finland during 2007-2018. A total of 11,397 eyes of 11,397 patients were examined. Kaplan-Meier and Cox regression analyses were used.

9. Results

In study I, 54 individuals had fundus changes and formed the AMD group, and 1,697 formed the non-AMD group. In the whole study population AMD patients had fewer teeth ($p<0.001$) and more alveolar bone loss ($p=0.004$). In a logistic regression model adjusted for age, smoking and diabetes, alveolar bone loss was associated with AMD in males (OR 4.3, CI 1.3-14.6, $p=0.013$). In the whole population the association between alveolar bone loss and AMD was lost. The association between the number of teeth and AMD in the whole population was also lost when the data were adjusted for age. In conclusion, periodontitis could be one risk factor for AMD in males.

In study II the number of anti-VEGF injections given in Finland increased from 60,412 in 2015 to 93,589 in 2017 (average annual change +24.5%). The number of aflibercept injections was 8,299 in 2015 rising to 20,833 in 2017 (average annual change +58.7%). Of the 43,996 aflibercept injections 30,364 (20.7% of total anti-VEGF injections) were given at university central hospitals and 13,362 (15.8% of total) at central hospitals during follow-up. Between 2015 and 2017 the use of ranibizumab was minimal, only 432 injections in 2015, 283 in 2016 and 216 in 2017. The PRN regimen was used as primary protocol at three university hospitals and 10 central hospitals. TER was the main protocol at two university hospitals and four central hospitals. During the study period the total and first line-treatment with bevacizumab did not correlate with new-onset visual impairment. However, the 3-year average for aflibercept injections correlated inversely with new-onset visual impairments. It was therefore concluded that aflibercept injections as a second-line treatment might help to prevent visual impairment.

The main finding from study III was that topical steroids administered after cataract surgery caused statistically significant lower rates of posterior capsular opacification (PCO) compared to non-steroidal anti-inflammatory drops (HR 0.76, 95% CI 0.62-0.93, p=0.009). Treatment with combination therapy (NSAID + topical steroids) provided no additional benefit over steroid monotherapy (HR 1.11, 95% CI 0.68-1.80, p=0.674). Cox regression analysis adjusted for age, sex, pseudoexfoliation, and risk stratification remained significantly predictive for lower capsulotomy rates (meaning lower PCO rates) with steroid treatment over the NSAID arm (HR 0.70, 95% CI 0.52-0.88, p=0.001). Secondary analyses revealed that patient age was inversely associated with Nd:YAG capsulotomy rates as the HR for Nd:YAG among patients older than 65 years was 0.58 compared to those under 65 years. Female gender was significantly associated with Nd:YAG capsulotomy rates. Poor mydriasis, pupil expansion device, DME or PDR were not associated with higher capsulotomy rates.

In study IV we examined 111 patients, mean age 78.9 years. At cataract surgery central subfield macular thickness (CSMT) was 280.1 ± 75.0 µm, postoperatively 268.6± 67.6 µm and after 1 year 265± 67.9 µm. Best corrected visual acuity (BCVA) (logMAR) was 0.70±0.46 prior to cataract surgery, 0.39±0.40 postoperatively and 0.33±0.34 1 year after surgery. The correlation between CSMT at cataract surgery and BCVA gain 1 year postoperatively was 0.312 r (logMAR) p=0.003. The cataract surgery did not significantly correlate with the incidence of hemorrhage, PED, IF or SRF when comparing macular status at surgery, postoperatively and at 1-year.

Cataract surgery had no effect on wet AMD activation or progression. The central subfield macular thickness continued to decrease after surgery. Neither topical nor systemic medication influenced the state of wet AMD. After 1 year the outcome of cataract surgery was the same irrespective of the number of anti-VEGF injections or treatment interval. The thicker the CSMT at surgery and the greater the postoperative resolution, the greater the BCVA gain.

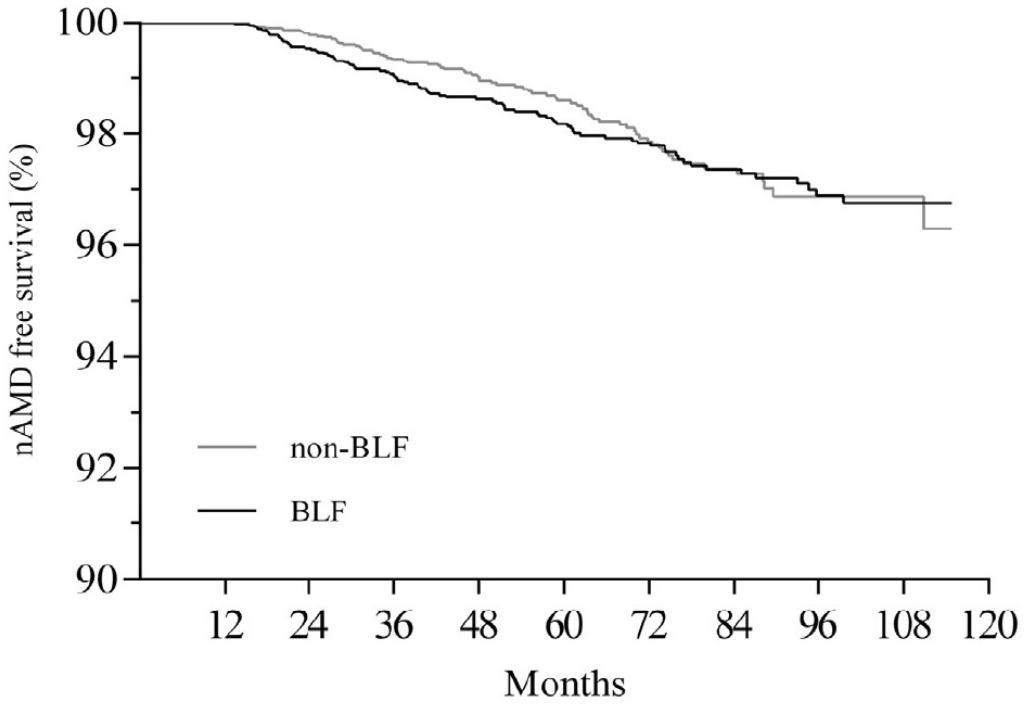
In study V the mean age of the subjects was 73.2 ± 9.9 years, comprising 61.8% females and 38.2% males. The mean follow-up time was 25.4 ± 16.8 months. Overall PCO rates were 1.1% at 1 year, 3.0% at 2 years, 7.1% at 3 years and 10.2% at 4 years. Patients with IOL diopters (D) in the lower quartile (≤ 20 D) had significantly higher rates of PCO (1.3% at 1 year, 4.4% at 2 years, 9.4% at 3 years and 14.2% at 4 years, p < .001). Logistic regression analysis showed an increased risk of PCO formation with lower diopter IOLs – for ≤ 20.0D OR 1.343 (95% CI: 1.132-1.593) and for ≤ 10 D: OR 2.409 (95% CI 1.203-

4.287), p < .001 for all comparisons. In a multivariant regression analysis accounting for possible confounders, the results were unchanged. Higher IOL diopters (> 28 D) did not correlate with higher PCO rates. It was concluded that the lower IOL power was associated with an increased risk of clinically significant PCO.

In study VI we examined 11,397 patients (mean age 75.4 ± 8.3 years) and 11,397 eyes. The study population comprised 37.5% males and 62.5% females. A blue-light filtering IOL was inserted in 5,425 (47.6%) eyes, and a non-blue-light filtering IOL in 5,972 (52.4%) eyes. The follow-up time in the blue-light filtering IOL group was 55.2 ± 34.1 months and in the non-blue-light filtering IOL group 50.5 ± 30.1 months. During follow-up, 164 new-onset neovascular AMD cases were recorded: 88 in the BLF group and 76 in the non-BLF group. Neovascular AMD-free survival was the same in both groups (p=0.465, log-rank test). In a Cox regression analysis controlling for age, gender, and a documented diagnosis of macular degeneration, the use of a BLF IOL did not predict neovascular AMD development (hazard ratio [HR], 1.075; 95% CI, 0.79-1.47; p=0.652).

Secondary clinical outcomes at 1 year in neovascular AMD patients were comparable for BCVA, foveal thickness, number of anti-VEGF injections, and treatment interval for BLF and non-BLF IOLs, respectively. For patients in whom wet AMD developed after cataract surgery and among patients with wet AMD before surgery (BLFn=71, non-BLF n=74) the clinical outcomes were the same (p> 0.05 in every case).

In conclusion, the BLF IOL and non-BLF IOL were the same in terms of new-onset wet AMD.



Number at Risk

Time-point	Baseline	One year	Two years	Three years	Four years	Five years	Six years	Seven years	Eight years	Nine years
BLF	5425	4602	4153	3568	2862	2405	1836	1322	896	326
Non-BLF	5972	5463	4537	3575	2943	2227	1536	1010	476	215

Figure 9. Survival plot (Kaplan-Meier) shows neovascular age-related macular degeneration-free survival time with BLF IOLs and non-BLF IOLs. No statistical significance difference was found between these IOLs.

DISCUSSION

Age-related macular degeneration has several risk factors (16 mentioned in one study), including tobacco smoking, advanced age, genetic susceptibility and low intake of antioxidants as well as high BMI, hypertension and history of cardiovascular disease (Chakravarthy et al. 2010). In cardiovascular disease the vasculature is stressed by the high concentrations of lipids and low-grade inflammation, which eventually leads to arteriosclerosis and oxidative stress of the heart musculature. No significant association was found in prospective cohort and cross-sectional studies, but a significant association was observed in the case control studies in cardiovascular disease and late AMD, OR 2.20 (95% CI 1.48 – 3.26). In a prospective cohort study diabetes was associated with late AMD, with RR 1.66 (95% CI, 1.05 – 2.63) (Chakravarthy et al. 2010). The mechanism of this might be hyperglycemia and hypoxia. Cigarette smoking has the same effect in addition to increasing platelet aggregation and fibrinogen levels. Smoking also lowers levels of high-density lipoproteins and antioxidants in the blood. Current smokers have a 1.9-fold increased risk of developing AMD, and ex-smokers a 1.7-fold risk. The risk of neovascular AMD was 2.6 OR (95% CI, 1.4 – 4.8) - 3.20 OR or geographic atrophy 4.54 - 4.8 (95%, 2.1 – 11.1) in current smokers, compared with 1.7 for ex-smokers (Smith et al. 1996; Chakravarthy et al. 2007). Fish intake and omega-3 fatty acids have been reported to protect against AMD (Smith et al. 2000; Seddon et al. 2003) while on the other hand a high-fat diet and obesity are risks for developing AMD, which should be kept in mind. Advanced age increases the relative risk of developing soft indistinct drusens by 14.2 (95% CI, 9.6, 21.2) in those 75 or older compared to those aged 43-54. Pigmentary changes, geographic atrophy and neovascular AMD also increase with age (Klein et al. 2020). The prevalence of late AMD is 7.0 – 12.0 times higher in those aged 80 and older (Chakravarthy et al. 2010).

The mechanism of degeneration of an aging retina might be caused by hypoxia, oxidative stress and autophagy malfunction (Blasiak et al. 2014). High BMI patients have been found to have 1.28 RR (CI 95%, 0.98-1.67) for late AMD (Chakravarthy et al. 2010). This might be due to low-grade inflammation (Wedell-Neergaard et al. 2018). In terms of race, it is important to remember that white women are at greater risk of early and late AMD than black women and white men (Fisher et al. 2016). On the other hand, individuals of native American ancestry were nearly 15 times more likely to have geographic atrophy than Latinos (Fraser-Bell et al. 2005). In this study a positive family history increases the risk of geographic atrophy 28 times. Siblings have been reported to have a three- to six-fold risk of developing AMD compared to the general population (Maller et al. 2006). This naturally suggests that genetics plays an important role in pathogenesis. Analysis of

prospective cohort studies showed that previous cataract surgery is a strong risk factor for neovascular AMD, 3.05 RR (CI 2.05 – 4.55) (Chakravarthy et al. 2010). However, our study (Karesvuo 2021) showed that cataract surgery did not cause new wet AMD cases or affect wet AMD status. One explanation could be surgery-induced intraocular inflammation. This inflammation might be too subtle so that the macula do not react to it. It could be suggested that cataract surgery can be performed for wet AMD patients without a major risk of activating the disease. On the other hand, in three case control studies hypertension has been shown to be associated with late AMD, OR 1.48 (95% CI, 1.22 – 1.78) (Chakravarthy et al. 2010).

We now suggest that periodontitis could be one risk factor for AMD (Karesvuo et al. 2013). In the study the OR 4.3 is fairly high, but it can be explained by the 1.3-14.6 confidence interval and the small number of study patients. The exact mechanism is still unknown, but this study gives new insight into the basic risk profile. Further and larger studies are needed to establish the association. The pathophysiology is complex and is still the subject of debate. Low-grade inflammation (Kauppinen et al. 2016) and mast cell degranulation (Ogura et al. 2020) are suggested to be possible reasons. In order to reduce the risk of developing AMD, good oral health is needed and can be achieved by teeth brushing twice a day and cleaning the interdental spaces. Attention should also be given to other risk factors, including quitting smoking, eating a healthy diet, treating hypertension and elevated cholesterols, exercise and losing weight. When there is wet AMD in one eye, the other eye has a 50% risk of developing wet AMD within five years. To reduce the risk, oral antioxidants plus (zinc) lutein and zeaxanthin are good options. The Mediterranean diet should also be considered when planning suitable meals.

The effect of cataract surgery in wet AMD patients is under debate and has been studied with conflicting results. Some studies suggest surgery should be avoided for six months from the diagnosis of wet AMD (Daien et al. 2018), others recommend surgery despite fluid on OCT (Starr et al. 2018). The use of topical anti-inflammatory drugs has been suggested for at least 3 weeks after uneventful cataract surgery in all patients to prevent PCME (Ylinen et al. 2018). Our study showed that cataract surgery does not cause or exacerbate wet AMD as the macula gets drier postoperatively with anti-VEGF therapy and 1 year after surgery. Postponing surgery is not preferable. However, our study (Karesvuo 2021) provides no evidence about the early intervention after diagnosis of wet AMD. Only seldom (3 of 111 patients) did CSMT increase by over 30% after surgery compared to CSMT before surgery. It can therefore be suggested that cataract surgery is safe for wet AMD patients when indicated and does not need to be postponed. One study (Daien et al. 2018)

recommended surgery 6 months after neovascular AMD diagnosis due to CNV activation and reduced vision gain. It is important to operate on the cataract early because it influences the patient's quality of life and the risk of accidents like hip fractures (Porela-Tiihonen et al. 2016). Cataract surgery is safe, has low complication rates, and an anesthetic can be used without activating wet AMD disease. Also, the follow-up of the disease is easier because of the better visibility of the fundus and higher quality OCT pictures. The type of cataract also affects the patient's symptoms, and a PSCC could cause significantly reduced vision, while a cortical cataract could result in a lot of glare. In conclusion, both reading vision and peripheral vision improve after surgery, and this helps the patient in everyday life.

Different intraocular lenses (IOLs) are used for patients in surgery, and studies have focused on blue-light filtering IOLs and non-BLF IOLs to find out if is there any difference between these lenses and whether it affects the occurrence of wet AMD. In our study there were no differences between these lenses. Blue light has been shown to be phototoxic to photoreceptors. In an aging eye the lens becomes yellow and absorbs more blue light and this is thought to naturally protect the retina. However, the effect on the retina may be only minimal, as demonstrated by a study on non-BLF and BLF IOLs (Achiron et al. 2020). This means that cataract surgery is equally safe for wet AMD patients when using non-BLF-IOLSs and BLF-IOLs.

Anti-VEGF therapy has opened up a new era in the treatment of neovascular AMD patients. Bevacizumab and ranibizumab have been shown to be effective in treating these patients, although since the CATT study the use of ranibizumab has fallen substantially (Pershing et al. 2019). Aflibercept is a good drug and its use as second-line treatment is popular in unresponsive cases. Aflibercept as second-line treatment might lower the incidence of new-onset visual impairment and make the treatment more successful. In addition, the fact that this drug has a longer effect relieves the treatment burden on patients and means greater cost-effectiveness for hospitals and taxpayers (Karesvuo et al. 2020).

PCO is one of the commonest complications of uneventful cataract surgery. Post-operative topical anti-inflammatory medication is generally used in almost every patient. The selection of medication is at the discretion of the physician. We compared the rate of PCO and three topical medication options (steroid, NSAID and their combination) after uneventful cataract surgery. Topical steroid medication after cataract surgery reduced the rate of PCO (Hecht et al. 2020), but its combination with topical NSAID yielded no additional benefit.

In our study the use of the lower IOL diopter correlated with an increased risk of PCO (Hecht et al. 2020), as also seen in other studies (Lindholm et al. 2020). One explanation for this could be the classical "no space no cell" theory. This means that the IOL is in contact with the posterior capsule and creates a barrier normally, but in lower IOL cases this might not happen or it is weaker due to the bigger and larger capsular bags of long myopic eyes (Peng et al. 2000). The velocity and type of capsular bend from the sharp edges of the IOL could also be one reason (Zhao et al. 2013). PCO worsens the patient's visual acuity and thus adversely affects quality of life. PCO is treated by Nd:YAG capsulotomy, which is a fairly quick and safe procedure with low complication rates. However, it uses valuable eyecare resources and could be avoided with proper IOL design and intraoperative procedures.

Periodontitis causes low-grade inflammation via inflamed periodontal tissue. Elevated levels of LPS, IL-6, IL-8, MMP-8, TNF-α and CRP are observed in the blood (Hegde & Awan 2019; Vitkov et al. 2021). In AMD one hypothesis is that there is loss of endothelial cells that make up the choriocapillaris (Crabb et al. 2002). Hypoxia of the choriocapillaris leads to secretion of ICAM-1 and VEGF from the choriocapillaris and RPE cells, which are associated with AMD (Skeie et al. 2010). Elevated levels of VCAM-1 and MCP-1 in vitreous humor have also been observed in exudative AMD even if VEGF levels are normal (Jonas et al. 2010). Endothelial cell permeability increases, mCRP accumulates in the choriocapillaris and inflammatory proteins are elevated (Chirco et al. 2016). It is our view that periodontal LPS penetrates through the eye's choriocapillaris with its numerous fenestrations and reacts with mast cells (Bhutto et al. 2016) and RPEs TLR2 and TLR4 (Palaska et al. 2016). Mast cells produce tryptase (Ogura et al. 2020) and the RPE produces excess amounts of IL-6 and IL-8 due to hypoxia and LPS influence (Arjamaa et al. 2017). The effect of LPS is long standing because of LPS seeding from chronic inflammation and infection of the periodontium. This causes slow degeneration of the RPE, Bruch's membrane and the choroid and eventually, according to our theory, leads to AMD.

Our study found a statistically significant correlation between alveolar bone loss and AMD in males (Karesvuo et al. 2013). However, the study is cross-sectional in design and AMD diagnosis is self-reported and the number of AMD cases (54) is quite small. Other studies (Brzozowska & Puchalska-Niedbał 2012; Wagley et al. 2015; Shin et al. 2017; Pockpa et al. 2019; Sun et al. 2019) have come to the same conclusions. Two recent systematic review articles (Javed et al. 2020; Lv et al. 2020) gave different results. Javed et al. argued there is too much bias in the studies and that a "true" correlation between these two diseases

could not be made. However, Lv et al. found a 35% risk of AMD in periodontitis patients. The subject and results are thus debatable and more and larger studies are needed. In the future the way to treat and prevent AMD could be through good oral hygiene. Not all cases of AMD can be prevented, but the low-grade inflammation burden would be diminished, which benefits the body as a whole. Treating periodontal disease and treating gum disease by means of anti-infective therapy and teeth brushing and even surgery in more advanced cases, is warranted. Anti-infective therapy removes calculus from interdental pockets. Teeth brushing twice a day is suggested, with an electric toothbrush being more effective in both short and long terms compared to a manual toothbrush (Yaacob et al. 2014; de Jager et al. 2017).

In conclusion, wet AMD, cataract and PCO cause visual impairment if left untreated. Our study gives uncertain results, but does suggest that periodontitis might be one risk factor for wet AMD. Our findings also indicate that cataracts can be operated on without causing exacerbation of wet AMD, and that aflibercept as second-line treatment might reduce the incidence of new-onset visual impairment. There is no difference between blue-light filtering and non-blue-light filtering IOL in terms of new-onset wet AMD. Steroid use after cataract surgery lowers the incidence of PCO as do lower power IOLs.

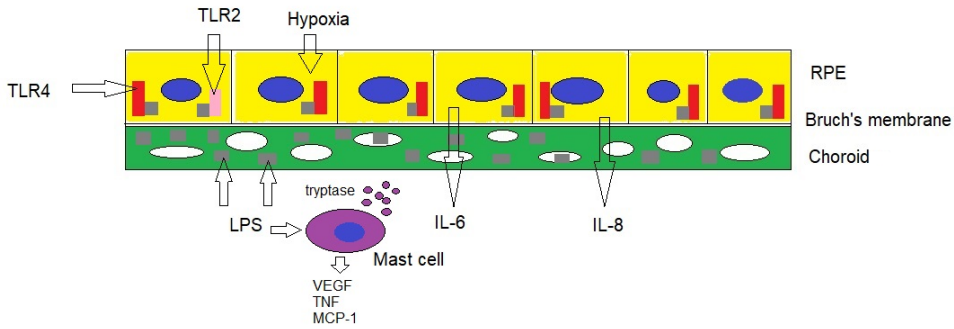


Figure 10. Retinal pigment epithelium, choroid, mast cells and lipopolysaccharides in interaction.

CONCLUSIONS

We believe that periodontitis might be one risk factor for AMD, possibly due to low-grade inflammation. In our study we concluded that aflibercept might reduce new-onset visual impairment. Our study also indicates that cataract surgery does not accelerate the progression of wet AMD. It was also shown that blue-light filtering IOLs are the same as non-blue-light filtering IOLs in terms of progression of wet AMD. According to our study postoperative steroid induced less PCO than non-steroidal drops, while low diopter IOLs resulted in more PCO than higher diopter IOLs.

YHTEENVETO (Finnish summary)

Kostea ikärappeuma on yli 65-vuotiaiden yleisin näkövammaisuuden syy teollistuneissa maissa. Uudet kasvutekijäestäjä hoidot ovat mullistaneet kostean ikärappeuman hoidon. Ongelmana on kuitenkin niiden lyhyt vaikutusaika eli pistoksia joudutaan antamaan potilaille kuukauden – kolmen kuukauden välein tilanteesta riippuen.

Harmaakaihi on puolestaan yleisin näkövammaisuuden syy kehittyvissä maissa. Kaihileikkaus on yksi yleisimmistä päiväkirurgisista toimenpiteistä ja sen on todettu olevan turvallinen, kustannustehokas, näöntarkkuutta ja elämänlaatua parantava toimenpide.

Harmaakaihi ja kostea ikärappeuma esiintyvät vanhusväestöllä ja usein ne esiintyvätkin yhtä aikaa. Eri tutkimukset ovat antaneet eriäviä tuloksia siitä pahentaako kaihileikkaus kostean ikärappeuman tilannetta. Tutkimuksessamme näin ei käynyt vaan kostea ikärappeuma osoitti rauhoittumisen merkkejä injektiohoitojen jatkuessa kaihileikkauksesta huolimatta.

Aflibercepti on uusi kasvutekijäestäjä lääke ja se on vaikutukseltaan pidempi kuin esimerkiksi bevacizumabi. Tutkimuksessamme huomasimme, että aflibercepti saattais vähentää näkövammaisuuden esiintyvyyttä.

Kaihileikkauksessa käytettävä paikallislääkitys leikkauksen jälkeen on todettu vähentävän komplikaatioita ja tutkimuksissamme totesimme, että kortisonilääke vähensi jälkikaihen esiintyvyyttä enemmän verrattuna NSAID lääkkeisiin.

Kaihileikkauksessa käytettäviä tekomykiötä on erilaisia, on sinivalosuodattavia ja ei-sinivaloasuodattavia. Eläinkokeissa sinivalon on todettu olevan haitallista verkkokalvolle, mutta tutkimuksessamme näiden linssien välillä ei ollut eroa, kun verrattiin uusien kostean ikärappeuma tapausten esiintyvyyttä.

Tekomykiön vahvuudella huomasimme olevan vaikutusta jälkikaihen esiintyvyyteen. Matalavahvuuksisilla tekomykiön saaneilla esiintyi enemmän jälkikaihea verrattuna normaalivahvuuksisiin ja korkeavahvuuksisiin tekomykiöihin.

Ikärappeuman tunnettuja riskitekijöitä ovat korkea ikä, sukurasitus ja tupakointi. Uutena tekijänä havaitsimme, että parodontiitti saattaisi olla uusi ikärappeuman riskitekijä.

SAMMANFATTNING (Swedish summary)

Våt åldersrelaterad makuladegeneration är den vanligaste orsaken till synskada hos människor över 65 år i industrialiserade länder. Nya tillväxtfaktorhämmare har revolutionerat behandlingen av våt åldersrelaterad makuladegeneration. Problemet med dem är att deras verkningstid är kort och de måste ges varje månad – eller vart tredje månad i ögat.

Gråstarr är den vanligaste orsaken till synskada och blindhet i utvecklingsländer. Starroperation är en vanlig dagkirurgisk åtgärd och den har konstaterats vara trygg och kostnadseffektiv.

Starr och åldersrelaterad makuladegeneration uppträder hos äldre och de uppträder ofta samtidigt. Olika studier har gett olika resultat när det gäller huruvida en starroperation försämrar våt åldersrelaterad makuladegeneration. Vår studie ledde till att det inte spelar någon roll om man opererar våt åldersrelaterad makuladegeneration.

Aflibercept är en ny tillväxtfaktorhämmare och den har längre verkningstid. Resultatet av vår studie är att aflibercept minskade förekomsten av synskada.

Vid starroperation används lokala mediciner som minskar postoperativa komplikationer. I vår studie var kortisondroppar effektivare när det gäller att minska efterstarr jämfört med NSAID droppar.

Vid starroperation använder man olika intraokulära linser, det finns blåljusfiltrerande och icke-blåljusfiltrerande linser. I djurstudier har man konstaterat att blåljus inte är bra för näthinnan, och i våra studier förekom det inte någon skillnad mellan dessa linser i frekvensen av ny våt åldersrelaterad makuladegeneration.

Vi konstaterade att styrkan hos en intraokulär lins påverkar frekvensen av efterstarr. Hos personer som fått intraokulära linser förekom mer efterstarr än hos dem med normal och hög styrka.

Riskfaktorerna för åldersrelaterad makuladegeneration är många, såsom hög ålder, ärftlighet och rökning. Vi fann att en ny riskfaktor, parodontit, infektion i tändernas stödvävnad, kunde ligga bakom åldersrelaterad makuladegeneration.

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REFERENCES

Aaronson A, A Achiron & R Tuuminen (2020): Clinical Course of Pseudophakic Cystoid Macular Edema Treated with Nepafenac. Journal of clinical medicine **9**.

Aaronson A, A Viljanen, P Kanclerz, A Grzybowski & R Tuuminen (2020): Cataract complications study: an analysis of adverse effects among 14,520 eyes in relation to surgical experience. Annals of translational medicine **8**: 1541.

Achiron A, U Elbaz, I Hecht, O Spierer, A Einan-Lifshitz, P Karesvuo, I Laine & R Tuuminen (2020): The Effect of Blue-Light Filtering Intraocular Lenses on the Development and Progression of Neovascular Age-related Macular Degeneration. Ophthalmology.

Agarwal A (2012): Gass' Atlas of Macular Diseases. **5th edition**.

Ahl DR, JL Hilgeman & JD Snyder (1986): Periodontal emergencies. Dental clinics of North America **30**: 459-472.

Alfonso JF, A Fernández-Vega-Cueto, B Alfonso-Bartolozzi, I Rodríguez-Uña & R Montés-Micó (2019): Visual And Refractive Outcomes In Hyperopic Pseudophakic Patients Implanted With A Trifocal Intraocular Lens. Clinical ophthalmology (Auckland, N.Z.) **13**: 2261-2268.

Altay U, CA Gürgan & K Ağbaht (2013): Changes in inflammatory and metabolic parameters after periodontal treatment in patients with and without obesity. Journal of periodontology **84**: 13-23.

AREDS (2001): A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Archives of ophthalmology (Chicago, Ill. : 1960) **119**: 1417-1436.

Arjamaa O, V Aaltonen, N Piippo, T Csont, G Petrovski, K Kaarniranta & A Kauppinen (2017): Hypoxia and inflammation in the release of VEGF and interleukins from human retinal pigment epithelial cells. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie **255**: 1757-1762.

Arjunan P, R Swaminathan, J Yuan, M Al-Shabrawey, DG Espinosa-Heidmann, J Nussbaum, PM Martin & CW Cutler (2020): Invasion of Human Retinal Pigment Epithelial Cells by Porphyromonas gingivalis leading to Vacuolar/Cytosolic localization and Autophagy dysfunction In-Vitro. Scientific reports **10**: 7468.

Armbrecht AM, C Findlay, PA Aspinall, AR Hill & B Dhillon (2003): Cataract surgery in patients with age-related macular degeneration: one-year outcomes. Journal of cataract and refractive surgery **29**: 686-693.

Asbell PA, I Dualan, J Mindel, D Brocks, M Ahmad & S Epstein (2005): Age-related cataract. Lancet (London, England) **365**: 599-609.

Augsburger M, GM Sarra & P Imesch (2019): Treat and extend versus pro re nata regimens of ranibizumab and aflibercept in neovascular age-related macular degeneration: a comparative study. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie **257**: 1889-1895.

Baatz H, R Darawsha, H Ackermann, GB Scharioth, D de Ortueta, M Pavlidis & LO Hattenbach (2008): Phacoemulsification does not induce neovascular age-related

macular degeneration. Investigative ophthalmology & visual science **49**: 1079-1083.
Baron A (1953): [Tolerance of the eye for plastic materials: prostheses for the cornea and crystalline lens]. Bulletin des societes d'ophtalmologie de France **9**: 982-988.
Battaglia Parodi M, P Iacono, A Papayannis, G Alto, A Buzzotta, A Arrigo, MV Cicinelli & F Bandello (2020): Near-infrared fundus autofluorescence in early age-related macular degeneration. European journal of ophthalmology **30**: 1448-1453.
Belloni L (1956): [Francesco Buzzi and the discovery of macula lutea]. L' Ospedale maggiore **44**: 223-234.
Berg K, TR Pedersen, L Sandvik & R Bragadóttir (2015): Comparison of ranibizumab and bevacizumab for neovascular age-related macular degeneration according to LUCAS treat-and-extend protocol. Ophthalmology **122**: 146-152.
Bhutto IA, DS McLeod, T Jing, JS Sunness, JM Seddon & GA Lutty (2016): Increased choroidal mast cells and their degranulation in age-related macular degeneration. The British journal of ophthalmology **100**: 720-726.
Bird AC, NM Bressler, SB Bressler, IH Chisholm, G Coscas, MD Davis, PT de Jong, CC Klaver, BE Klein, R Klein & et al. (1995): An international classification and grading system for age-related maculopathy and age-related macular degeneration. The International ARM Epidemiological Study Group. Survey of ophthalmology **39**: 367-374.
Blair CJ (1975): Geographic atrophy of the retinal pigment epithelium. A manifestation of senile macular degeneration. Archives of ophthalmology (Chicago, Ill. : 1960) **93**: 19-25.
Blasiak J, G Petrovski, Z Veréb, A Facskó & K Kaarniranta (2014): Oxidative stress, hypoxia, and autophagy in the neovascular processes of age-related macular degeneration. BioMed research international **2014**: 768026.
Bockelbrink A, S Roll, K Ruether, A Rasch, W Greiner & SN Willich (2008): Cataract surgery and the development or progression of age-related macular degeneration: a systematic review. Survey of ophthalmology **53**: 359-367.
Boiché M, K Angioi-Duprez, JB Conart & JP Berrod (2019): Treatment of hematomas in age related macular degeneration by vitrectomy and subretinal injection of r-tPA: Preliminary results. Journal francais d'ophtalmologie **42**: e391-e397.
Borooah S, PY Sim, S Phatak, G Moraes, CY Wu, CMG Cheung, B Pal & D Bujarborua (2020): Pachychoroid spectrum disease. Acta ophthalmologica.
Brancato R, U Introini, G Bolognesi, G Pacelli, G Trabucchi & A Pece (2000): ICGA-guided laser photocoagulation of occult choroidal neovascularization in age-related macular degeneration. Indocyanine green angiography. Retina (Philadelphia, Pa.) **20**: 134-142.
Brynskov T, IC Munch, TM Larsen, L Erngaard & TL Sørensen (2020): Real-world 10-year experiences with intravitreal treatment with ranibizumab and aflibercept for neovascular age-related macular degeneration. Acta ophthalmologica **98**: 132-138.
Brzozowska A & L Puchalska-Niedbał (2012): [Oral status as a potential source of infection in AMD patients--introduction]. Klinika oczna **114**: 29-32.
Bunce C, W Xing & R Wormald (2010): Causes of blind and partial sight certifications in England and Wales: April 2007-March 2008. Eye (London, England) **24**: 1692-1699.

Cackett P, I Yeo, CM Cheung, EN Vithana, D Wong, WT Tay, ES Tai, T Aung & TY Wong (2011): Relationship of smoking and cardiovascular risk factors with polypoidal choroidal vasculopathy and age-related macular degeneration in Chinese persons. Ophthalmology **118**: 846-852.

Cardoso EM, C Reis & MC Manzanares-Céspedes (2018): Chronic periodontitis, inflammatory cytokines, and interrelationship with other chronic diseases. Postgraduate medicine **130**: 98-104.

Cataracts (2019): Current Care Guideline: the Finnish Medical Society Duodecim 2019.

Chakravarthy U, C Augood, GC Bentham, PT de Jong, M Rahu, J Seland, G Soubrane, L Tomazzoli, F Topouzis, JR Vingerling, J Vioque, IS Young & AE Fletcher (2007): Cigarette smoking and age-related macular degeneration in the EUREYE Study. Ophthalmology **114**: 1157-1163.

Chakravarthy U, RF Houston & DB Archer (1993): Treatment of age-related subfoveal neovascular membranes by teletherapy: a pilot study. The British journal of ophthalmology **77**: 265-273.

Chakravarthy U, TY Wong, A Fletcher, E Piault, C Evans, G Zlateva, R Buggage, A Pleil & P Mitchell (2010): Clinical risk factors for age-related macular degeneration: a systematic review and meta-analysis. BMC ophthalmology **10**: 31.

Chan CK, P Abraham, CH Meyer, GT Kokame, PK Kaiser, ME Rauser, JG Gross, AS Nuthi, SG Lin & NS Daher (2010): Optical coherence tomography-measured pigment epithelial detachment height as a predictor for retinal pigment epithelial tears associated with intravitreal bevacizumab injections. Retina (Philadelphia, Pa.) **30**: 203-211.

Chan CK, CH Meyer, JG Gross, P Abraham, AS Nuthi, GT Kokame, SG Lin, ME Rauser & PK Kaiser (2007): Retinal pigment epithelial tears after intravitreal bevacizumab injection for neovascular age-related macular degeneration. Retina (Philadelphia, Pa.) **27**: 541-551.

Chang YS, JH Kim, SJ Yoo, YJ Lew & J Kim (2016): Fellow-eye neovascularization in unilateral retinal angiomatous proliferation in a Korean population. Acta ophthalmologica **94**: e49-53.

Charbel Issa P, MC Gillies, EY Chew, AC Bird, TF Heeren, T Peto, FG Holz & HP Scholl (2013): Macular telangiectasia type 2. Progress in retinal and eye research **34**: 49-77.

Cheung CMG, JJ Arnold, FG Holz, KH Park, TYY Lai, M Larsen, P Mitchell, K Ohno-Matsui, SJ Chen, S Wolf & TY Wong (2017): Myopic Choroidal Neovascularization: Review, Guidance, and Consensus Statement on Management. Ophthalmology **124**: 1690-1711.

Cheung CMG, TYY Lai, P Ruamviboonsuk, SJ Chen, Y Chen, KB Freund, F Gomi, AH Koh, WK Lee & TY Wong (2018): Polypoidal Choroidal Vasculopathy: Definition, Pathogenesis, Diagnosis, and Management. Ophthalmology **125**: 708-724.

Chew EY, TE Clemons, E Agrón, RD Sperduto, JP Sangiovanni, N Kurinij & MD Davis (2013): Long-term effects of vitamins C and E, β-carotene, and zinc on age-related macular degeneration: AREDS report no. 35. Ophthalmology **120**: 1604-1611.e1604.

Chirco KR, SS Whitmore, K Wang, LA Potempa, JA Halder, EM Stone, BA Tucker & RF Mullins (2016): Monomeric C-reactive protein and inflammation in age-related macular degeneration. The Journal of pathology **240**: 173-183.

Chung YR, EJ Seo, YH Kim, H Yang & K Lee (2016): Hypertension as a risk factor for recurrent subretinal hemorrhage in polypoidal choroidal vasculopathy. Canadian journal of ophthalmology. Journal canadien d'ophtalmologie **51**: 348-353.

Ciombor KK, J Berlin & E Chan (2013): Aflibercept. Clinical cancer research : an official journal of the American Association for Cancer Research **19**: 1920-1925.

Clemens CR, N Bastian, F Alten, C Milojcic, P Heiduschka & N Eter (2014): Prediction of retinal pigment epithelial tear in serous vascularized pigment epithelium detachment. Acta ophthalmologica **92**: e50-56.

Clemens CR, A Wolf, F Alten, C Milojcic, P Heiduschka & N Eter (2017): Response of vascular pigment epithelium detachment due to age-related macular degeneration to monthly treatment with ranibizumab: the prospective, multicentre RECOVER study. Acta ophthalmologica **95**: 683-689.

Crabb JW, M Miyagi, X Gu, K Shadrach, KA West, H Sakaguchi, M Kamei, A Hasan, L Yan, ME Rayborn, RG Salomon & JG Hollyfield (2002): Drusen proteome analysis: an approach to the etiology of age-related macular degeneration. Proceedings of the National Academy of Sciences of the United States of America **99**: 14682-14687.

Cugati S, P Mitchell, E Rochtchina, AG Tan, W Smith & JJ Wang (2006): Cataract surgery and the 10-year incidence of age-related maculopathy: the Blue Mountains Eye Study. Ophthalmology **113**: 2020-2025.

Daien V, V Nguyen, N Morlet, JJ Arnold, RW Essex, S Young, A Hunyor, MC Gillies & D Barthelmes (2018): Outcomes and Predictive Factors After Cataract Surgery in Patients With Neovascular Age-related Macular Degeneration. The Fight Retinal Blindness! Project. American journal of ophthalmology **190**: 50-57.

Dansingani KK, O Gal-Or, SR Sadda, LA Yannuzzi & KB Freund (2018): Understanding aneurysmal type 1 neovascularization (polypoidal choroidal vasculopathy): a lesson in the taxonomy of 'expanded spectra' - a review. Clinical & experimental ophthalmology **46**: 189-200.

Davis MD, RE Gangnon, LY Lee, LD Hubbard, BE Klein, R Klein, FL Ferris, SB Bressler & RC Milton (2005): The Age-Related Eye Disease Study severity scale for age-related macular degeneration: AREDS Report No. 17. Archives of ophthalmology (Chicago, Ill. : 1960) **123**: 1484-1498.

de Jager M, A Rmaile, O Darch & JW Bikker (2017): The Effectiveness of Manual versus High-Frequency, High-Amplitude Sonic Powered Toothbrushes for Oral Health: A Meta-Analysis. The Journal of clinical dentistry **28**: A13-28.

de Molon RS, C Rossa, Jr., RM Thurlings, JA Cirelli & MI Koenders (2019): Linkage of Periodontitis and Rheumatoid Arthritis: Current Evidence and Potential Biological Interactions. International journal of molecular sciences **20**.

Deas DE, AJ Moritz, RS Sagun, Jr., SF Gruwell & CA Powell (2016): Scaling and root planing vs. conservative surgery in the treatment of chronic periodontitis. Periodontology 2000 **71**: 128-139.

Dick HB, M Tehrani & S Aliyeva (2004): Contrast sensitivity after implantation of toric iris-claw lenses in phakic eyes. Journal of cataract and refractive surgery **30**: 2284-2289.

Donders FC (1855): Beiträge zur pathologischen Anatomie des Auges. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie **1**: 106-118.

Dong LM, WJ Stark, JL Jefferys, S Al-Hazzaa, SB Bressler, SD Solomon & NM Bressler (2009): Progression of age-related macular degeneration after cataract surgery. Archives of ophthalmology (Chicago, Ill. : 1960) **127**: 1412-1419.
Downie LE, L Busija & PR Keller (2018): Blue-light filtering intraocular lenses (IOLs) for protecting macular health. The Cochrane database of systematic reviews **5**: Cd011977.
Duker MYJS (2009): Ophthalmology. Mosby Elsevier.
Ehinger B & A Grzybowski (2011): Allvar Gullstrand (1862-1930)--the gentleman with the lamp. Acta ophthalmologica **89**: 701-708.
Errera MH, SE Liyanage, P Petrou, PA Keane, R Moya, E Ezra, DG Charteris & L Wickham (2018): A Study of the Natural History of Vitreomacular Traction Syndrome by OCT. Ophthalmology **125**: 701-707.
Ersoz MG, M Karacorlu, S Arf, I Sayman Muslubas & M Hocaoglu (2017): Retinal pigment epithelium tears: Classification, pathogenesis, predictors, and management. Survey of ophthalmology **62**: 493-505.
Falck A, P Virtanen & A Tuulonen (2012): Is more always better in cataract surgery? Acta ophthalmologica **90**: e653-654.
Farecki ML, M Gutfleisch, H Faatz, K Rothaus, B Heimes, G Spital, A Lommatzsch & D Pauleikhoff (2017): Characteristics of type 1 and 2 CNV in exudative AMD in OCT-Angiography. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie **255**: 913-921.
Ferrara N, HP Gerber & J LeCouter (2003): The biology of VEGF and its receptors. Nature medicine **9**: 669-676.
Ferris FL, 3rd, CP Wilkinson, A Bird, U Chakravarthy, E Chew, K Csaky & SR Sadda (2013): Clinical classification of age-related macular degeneration. Ophthalmology **120**: 844-851.
Fisher DE, BE Klein, TY Wong, JI Rotter, X Li, S Shrager, GL Burke, R Klein & MF Cotch (2016): Incidence of Age-Related Macular Degeneration in a Multi-Ethnic United States Population: The Multi-Ethnic Study of Atherosclerosis. Ophthalmology **123**: 1297-1308.
Flaxman SR, RRA Bourne, S Resnikoff, P Ackland, T Braithwaite, MV Cicinelli, A Das, JB Jonas, J Keeffe, JH Kempen, J Leasher, H Limburg, K Naidoo, K Pesudovs, A Silvester, GA Stevens, N Tahhan, TY Wong & HR Taylor (2017): Global causes of blindness and distance vision impairment 1990-2020: a systematic review and meta-analysis. The Lancet. Global health **5**: e1221-e1234.
Fleckenstein M, P Mitchell, KB Freund, S Sadda, FG Holz, C Brittain, EC Henry & D Ferrara (2018): The Progression of Geographic Atrophy Secondary to Age-Related Macular Degeneration. Ophthalmology **125**: 369-390.
Frank RN, JE Puklin, C Stock & LA Canter (2000): Race, iris color, and age-related macular degeneration. Transactions of the American Ophthalmological Society **98**: 109-115; discussion 115-107.
Fraser-Bell S, J Donofrio, J Wu, R Klein, SP Azen & R Varma (2005): Sociodemographic factors and age-related macular degeneration in Latinos: the Los Angeles Latino Eye Study. American journal of ophthalmology **139**: 30-38.
Fritsche LG, W Igl, JN Bailey, F Grassmann, S Sengupta, JL Bragg-Gresham, KP Burdon, SJ Hebbring, C Wen, M Gorski, IK Kim, D Cho, D Zack, E Souied, HP Scholl, E

Bala, KE Lee, DJ Hunter, RJ Sardell, P Mitchell, JE Merriam, V Cipriani, JD Hoffman, T Schick, YT Lechanteur, RH Guymer, MP Johnson, Y Jiang, CM Stanton, GH Buitendijk, X Zhan, AM Kwong, A Boleda, M Brooks, L Gieser, R Ratnapriya, KE Branham, JR Foerster, JR Heckenlively, MI Othman, BJ Vote, HH Liang, E Souzeau, IL McAllister, T Isaacs, J Hall, S Lake, DA Mackey, IJ Constable, JE Craig, TE Kitchner, Z Yang, Z Su, H Luo, D Chen, H Ouyang, K Flagg, D Lin, G Mao, H Ferreyra, K Stark, CN von Strachwitz, A Wolf, C Brandl, G Rudolph, M Olden, MA Morrison, DJ Morgan, M Schu, J Ahn, G Silvestri, EE Tsironi, KH Park, LA Farrer, A Orlin, A Brucker, M Li, CA Curcio, S Mohand-Saïd, JA Sahel, I Audo, M Benchaboune, AJ Cree, CA Rennie, SV Goverdhan, M Grunin, S Hagbi-Levi, P Campochiaro, N Katsanis, FG Holz, F Blond, H Blanché, JF Deleuze, RP Igo, Jr., B Truitt, NS Peachey, SM Meuer, CE Myers, EL Moore, R Klein, MA Hauser, EA Postel, MD Courtenay, SG Schwartz, JL Kovach, WK Scott, G Liew, AG Tan, B Gopinath, JC Merriam, RT Smith, JC Khan, H Shahid, AT Moore, JA McGrath, R Laux, MA Brantley, Jr., A Agarwal, L Ersoy, A Caramoy, T Langmann, NT Saksens, EK de Jong, CB Hoyng, MS Cain, AJ Richardson, TM Martin, J Blangero, DE Weeks, B Dhillon, CM van Duijn, KF Doheny, J Romm, CC Klaver, C Hayward, MB Gorin, ML Klein, PN Baird, AI den Hollander, S Fauser, JR Yates, R Allikmets, JJ Wang, DA Schaumberg, BE Klein, SA Hagstrom, I Chowers, AJ Lotery, T Léveillard, K Zhang, MH Brilliant, AW Hewitt, A Swaroop, EY Chew, MA Pericak-Vance, M DeAngelis, D Stambolian, JL Haines, SK Iyengar, BH Weber, GR Abecasis & IM Heid (2016): A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants. Nature genetics **48**: 134-143.

Fujimoto J & E Swanson (2016): The Development, Commercialization, and Impact of Optical Coherence Tomography. Investigative ophthalmology & visual science **57**: Oct1-oct13.

Galvão EL, EM da Silveira, ES de Oliveira, TMM da Cruz, OD Flecha, SGM Falci & PF Gonçalves (2019): Association between mandibular third molar position and the occurrence of pericoronitis: A systematic review and meta-analysis. Archives of oral biology **107**: 104486.

Gass JD (1967): Pathogenesis of disciform detachment of the neuroepithelium. American journal of ophthalmology **63**: Suppl:1-139.

Gass JD (1970): Stereoscopic Atlas of Macular Diseases: A Funduscopic and Angiographic Presentation.

Gass JD (1984): Retinal pigment epithelial rip during krypton red laser photocoagulation. American journal of ophthalmology **98**: 700-706.

Gass JD (1988): Idiopathic senile macular hole. Its early stages and pathogenesis. Archives of ophthalmology (Chicago, Ill. : 1960) **106**: 629-639.

Gass JD (2003): Drusen and disciform macular detachment and degeneration. 1972. Retina (Philadelphia, Pa.) **23**: 409-436.

Gass JD, A Agarwal, AM Lavina & KA Tawansy (2003): Focal inner retinal hemorrhages in patients with drusen: an early sign of occult choroidal neovascularization and chorioretinal anastomosis. Retina (Philadelphia, Pa.) **23**: 741-751.

Gass JD & EW Norton (1969): Follow-up study of cystoid macular edema following cataract extraction. Transactions - American Academy of Ophthalmology and

Otolaryngology. American Academy of Ophthalmology and Otolaryngology **73**: 665-682.
Gelisken F, F Ziemssen, M Voelker, KU Bartz-Schmidt & W Inhoffen (2009): Retinal pigment epithelial tears after single administration of intravitreal bevacizumab for neovascular age-related macular degeneration. Eye (London, England) **23**: 694-702.
Gillies MC, AP Hunyor, JJ Arnold, RH Guymer, S Wolf, P Ng, FL Pecheur & IL McAllister (2019): Effect of Ranibizumab and Aflibercept on Best-Corrected Visual Acuity in Treat-and-Extend for Neovascular Age-Related Macular Degeneration: A Randomized Clinical Trial. JAMA ophthalmology **137**: 372-379.
Gomes-Filho IS, SSD Cruz, SC Trindade, JS Passos-Soares, PC Carvalho-Filho, A Figueiredo, AO Lyrio, AM Hintz, MG Pereira & F Scannapieco (2020): Periodontitis and respiratory diseases: A systematic review with meta-analysis. Oral diseases **26**: 439-446.
Gomi F & Y Tano (2008): Polypoidal choroidal vasculopathy and treatments. Current opinion in ophthalmology **19**: 208-212.
Gragoudas ES, AP Adamis, ET Cunningham, Jr., M Feinsod & DR Guyer (2004): Pegaptanib for neovascular age-related macular degeneration. The New England journal of medicine **351**: 2805-2816.
Gross NE, A Aizman, A Brucker, JM Klancnik, Jr. & LA Yannuzzi (2005): Nature and risk of neovascularization in the fellow eye of patients with unilateral retinal angiomatous proliferation. Retina (Philadelphia, Pa.) **25**: 713-718.
Grzybowski A & FJ Ascaso (2014): Sushruta in 600 B.C. introduced extraocular expulsion of lens material. Acta ophthalmologica **92**: 194-197.
Gökce SE, JH Zeiter, MP Weikert, DD Koch, W Hill & L Wang (2017): Intraocular lens power calculations in short eyes using 7 formulas. Journal of cataract and refractive surgery **43**: 892-897.
Haab O (1885): Erkrankungen der Macula lutea. Centralblatt fur Praktische Augenheilkunde.

: 383-384.
Haddad WM, G Coscas & G Soubrane (2002): Eligibility for treatment and angiographic features at the early stage of exudative age related macular degeneration. The British journal of ophthalmology **86**: 663-669.
Haigis W (2009): Intraocular lens calculation in extreme myopia. Journal of cataract and refractive surgery **35**: 906-911.
Hartmann KI, SF Oster, P Amini, DU Bartsch, L Cheng & WR Freeman (2015): SLO-Microperimetry in Wet Age-Related Macular Degeneration During Anti-VEGF Therapy. Ophthalmic surgery, lasers & imaging retina **46**: 824-830.
Hecht I, B Dubinsky-Pertzov, P Karesvuo, A Achiron & R Tuuminen (2020): Association between intraocular lens diopter and posterior capsular opacification. Clinical & experimental ophthalmology.
Hecht I, P Karesvuo, A Achiron, U Elbaz, I Laine & R Tuuminen (2020): Anti-inflammatory Medication After Cataract Surgery and Posterior Capsular Opacification. American journal of ophthalmology **215**: 104-111.
Hegde R & KH Awan (2019): Effects of periodontal disease on systemic health. Disease-a-month : DM **65**: 185-192.

Heier JS, DM Brown, V Chong, JF Korobelnik, PK Kaiser, QD Nguyen, B Kirchhof, A Ho, Y Ogura, GD Yancopoulos, N Stahl, R Vitti, AJ Berliner, Y Soo, M Anderesi, G Groetzbach, B Sommerauer, R Sandbrink, C Simader & U Schmidt-Erfurth (2012): Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology **119**: 2537-2548.

Hernandez L, T Lanitis, C Cele, H Toro-Diaz, A Gibson & A Kuznik (2018): Intravitreal Aflibercept Versus Ranibizumab for Wet Age-Related Macular Degeneration: A Cost-Effectiveness Analysis. Journal of managed care & specialty pharmacy **24**: 608-616.

Herrera D, B Alonso, L de Arriba, I Santa Cruz, C Serrano & M Sanz (2014): Acute periodontal lesions. Periodontology 2000 **65**: 149-177.

Hibbs SP, A Smith, LP Chow & SM Downes (2011): Colour photographs for screening in neovascular age-related macular degeneration: are they necessary? Eye (London, England) **25**: 918-921.

Holz FG, MS Figueroa, F Bandello, Y Yang, M Ohji, H Dai, H Wykrota, S Sharma, C Dunger-Baldauf, S Lacey, W Macfadden & P Mitchell (2020): RANIBIZUMAB TREATMENT IN TREATMENT-NAIVE NEOVASCULAR AGE-RELATED MACULAR DEGENERATION: Results From LUMINOUS, a Global Real-World Study. Retina (Philadelphia, Pa.) **40**: 1673-1685.

Hopley C, G Salkeld & P Mitchell (2004): Cost utility of photodynamic therapy for predominantly classic neovascular age related macular degeneration. The British journal of ophthalmology **88**: 982-987.

Hsu MY, YC Hung, DK Hwang, SC Lin, KH Lin, CY Wang, HY Choi, YP Wang & CM Cheng (2016): Detection of aqueous VEGF concentrations before and after intravitreal injection of anti-VEGF antibody using low-volume sampling paper-based ELISA. Scientific reports **6**: 34631.

Ikawa T, K Mizutani, T Sudo, C Kano, Y Ikeda, T Akizuki, H Kobayashi, Y Izumi & T Iwata (2021): Clinical comparison of an electric-powered ionic toothbrush and a manual toothbrush in plaque reduction: A randomized clinical trial. International journal of dental hygiene **19**: 93-98.

Isola V, A Pece & MB Parodi (2006): Choroidal ischemia after photodynamic therapy with verteporfin for choroidal neovascularization. American journal of ophthalmology **142**: 680-683.

Jackson TL, C Soare, C Petrarca, A Simpson, JE Neffendorf, R Petrarca, A Muldrew, T Peto, U Chakravarthy, L Membrey, R Haynes, M Costen, D Steel & R Desai (2020): Evaluation of Month-24 Efficacy and Safety of Epimacular Brachytherapy for Previously Treated Neovascular Age-Related Macular Degeneration: The MERLOT Randomized Clinical Trial. JAMA ophthalmology **138**: 835-842.

Jaffe NS (1996): History of cataract surgery. Ophthalmology **103**: S5-16.

Jaisankar D, G Swaminathan, R Roy, V Kulothungan, T Sharma & R Raman (2018): Association of obesity and age-related macular degeneration in Indian population. Indian journal of ophthalmology **66**: 976-983.

Javed F, A Sculean & GE Romanos (2020): Association between age-related macular degeneration and periodontal and peri-implant diseases: a systematic review. Acta ophthalmologica.

Jonas JB, Y Tao, M Neumaier & P Findeisen (2010): Monocyte chemoattractant protein 1, intercellular adhesion molecule 1, and vascular cell adhesion molecule 1 in

exudative age-related macular degeneration. Archives of ophthalmology (Chicago, Ill. : 1960) **128**: 1281-1286.
Jutley G, G Jutley, V Tah, D Lindfield & G Menon (2011): Treating peripapillary choroidal neovascular membranes: a review of the evidence. Eye (London, England) **25**: 675-681.
Kanski JJ (2007): Clinical Ophthalmology A systematic approach. Elsevier.
Karesvuo P, Elbaz U, Achiron A,, Hecht I, Kaarniranta K, Tuuminen R (2021): Effect of cataract surgery on wet age-related macular degeneration activity. . Acta ophthalmologica.
Karesvuo P, UK Gursoy, PJ Pussinen, AL Suominen, S Huumonen, E Vesti & E Könönen (2013): Alveolar bone loss associated with age-related macular degeneration in males. Journal of periodontology **84**: 58-67.
Karesvuo P, L Hakkala, K Kaarniranta, H Uusitalo, M Ojamo & R Tuuminen (2020): Correlation between the rate of intravitreal injections, use of aflibercept as a second-line treatment and visual impairment for wet AMD in Finland. Acta ophthalmologica.
Karma A (1986): Silmämuutokset eräissä immunologisissa yleissairauksissa. DUODECIM **102**: 1322-1334.
Kauppinen A, JJ Paterno, J Blasiak, A Salminen & K Kaarniranta (2016): Inflammation and its role in age-related macular degeneration. Cellular and molecular life sciences : CMLS **73**: 1765-1786.
Keenan TD, E Agrón, J Mares, TE Clemons, F van Asten, A Swaroop & EY Chew (2020): Adherence to the Mediterranean Diet and Progression to Late Age-Related Macular Degeneration in the Age-Related Eye Disease Studies 1 and 2. Ophthalmology.
Kennedy JE, MP Flaherty, AB Hunyor & LP Robinson (1985): Evaluation of nine hundred and sixty-seven consecutive intraocular implants. Australian and New Zealand journal of ophthalmology **13**: 349-354.
Klein R, BE Klein, SC Jensen & KJ Cruickshanks (1998): The relationship of ocular factors to the incidence and progression of age-related maculopathy. Archives of ophthalmology (Chicago, Ill. : 1960) **116**: 506-513.
Klein R, BE Klein, TY Wong, SC Tomany & KJ Cruickshanks (2002): The association of cataract and cataract surgery with the long-term incidence of age-related maculopathy: the Beaver Dam eye study. Archives of ophthalmology (Chicago, Ill. : 1960) **120**: 1551-1558.
Klein R, BEK Klein & KLP Linton (2020): Prevalence of Age-related Maculopathy: The Beaver Dam Eye Study. Ophthalmology **127**: S122-s132.
Klein R, MD Knudtson, BE Klein, TY Wong, MF Cotch, K Liu, CY Cheng, GL Burke, MF Saad, DR Jacobs, Jr. & AR Sharrett (2008): Inflammation, complement factor h, and age-related macular degeneration: the Multi-ethnic Study of Atherosclerosis. Ophthalmology **115**: 1742-1749.
Klein R, SM Meuer, CE Myers, GH Buitendijk, E Rochtchina, F Choudhury, PT de Jong, R McKean-Cowdin, SK Iyengar, X Gao, KE Lee, JR Vingerling, P Mitchell, CC Klaver, JJ Wang & BE Klein (2014): Harmonizing the classification of age-related macular degeneration in the three-continent AMD consortium. Ophthalmic epidemiology **21**: 14-23.
Kramer M, K Mimouni, E Priel, Y Yassur & D Weinberger (2000): Comparison of fluorescein angiography and indocyanine green angiography for imaging of

choroidal neovascularization in hemorrhagic age-related macular degeneration. American journal of ophthalmology **129**: 495-500.
Krogh Nielsen M, Y Subhi, CR Molbech, MK Falk, MH Nissen & TL Sørensen (2019): Systemic Levels of Interleukin-6 Correlate With Progression Rate of Geographic Atrophy Secondary to Age-Related Macular Degeneration. Investigative ophthalmology & visual science **60**: 202-208.
Kumar JB, S Stinnett, JIL Han & GJ Jaffe (2020): CORRELATION OF SUBRETINAL HYPERREFLECTIVE MATERIAL MORPHOLOGY AND VISUAL ACUITY IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION. Retina (Philadelphia, Pa.) **40**: 845-856.
Kvannli L & J Krohn (2017): Switching from pro re nata to treat-and-extend regimen improves visual acuity in patients with neovascular age-related macular degeneration. Acta ophthalmologica **95**: 678-682.
Laatikainen L & H Hirvelä (1995): Prevalence and visual consequences of macular changes in a population aged 70 years and older. Acta ophthalmologica Scandinavica **73**: 105-110.
Laitinen A, L Laatikainen, T Härkänen, S Koskinen, A Reunanen & A Aromaa (2010): Prevalence of major eye diseases and causes of visual impairment in the adult Finnish population: a nationwide population-based survey. Acta ophthalmologica **88**: 463-471.
Lalwani GA, PJ Rosenfeld, AE Fung, SR Dubovy, S Michels, W Feuer, JL Davis, HW Flynn, Jr. & M Esquiabro (2009): A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO Study. American journal of ophthalmology **148**: 43-58.e41.
Larry B (2007): Surgical Techiques in Ophthalmology. Cataract surgery. Saunders Elsevier.
Lau T, IY Wong, L Iu, J Chhablani, T Yong, K Hideki, J Lee & R Wong (2015): En-face optical coherence tomography in the diagnosis and management of age-related macular degeneration and polypoidal choroidal vasculopathy. Indian journal of ophthalmology **63**: 378-383.
Lee Kim E, KW Jeng-Miller & Y Yonekawa (2017): Macular Telangiectasia Type 1. Ophthalmology. Retina **1**: 381.
Leffler CT, SG Schwartz, E Peterson & J Busscher (2018): Cataract couching and the goat's eye. Acta ophthalmologica **96**: 755-756.
Leinonen MT & L Hyvärinen (2008): Documenting fixation at an extrafoveal locus with a modified slit lamp in age-related macular degeneration. Investigative ophthalmology & visual science **49**: 5274-5278.
Leitritz M, F Gelisken, W Inhoffen, M Voelker & F Ziemssen (2008): Can the risk of retinal pigment epithelium tears after bevacizumab treatment be predicted? An optical coherence tomography study. Eye (London, England) **22**: 1504-1507.
Lim LS, P Mitchell, JM Seddon, FG Holz & TY Wong (2012): Age-related macular degeneration. Lancet (London, England) **379**: 1728-1738.
Lim TH, TYY Lai, K Takahashi, TY Wong, LJ Chen, P Ruamviboonsuk, CS Tan, WK Lee, CMG Cheung, NF Ngah, R Patalauskaite, P Margaron & A Koh (2020): Comparison of Ranibizumab With or Without Verteporfin Photodynamic Therapy for Polypoidal Choroidal Vasculopathy: The EVEREST II Randomized Clinical Trial. JAMA ophthalmology.

Lindholm JM, I Laine & R Tuuminen (2020): Intraocular Lens Power, Myopia, and the Risk of Nd:YAG Capsulotomy after 15,375 Cataract Surgeries. Journal of clinical medicine **9**.

Little HL, HC Zweng & RR Peabody (1970): Argon laser slit-lamp retinal photocoagulation. Transactions - American Academy of Ophthalmology and Otolaryngology. American Academy of Ophthalmology and Otolaryngology **74**: 85-97.

Loewenstein A, R Malach, M Goldstein, I Leibovitch, A Barak, E Baruch, Y Alster, O Rafaeli, I Avni & Y Yassur (2003): Replacing the Amsler grid: a new method for monitoring patients with age-related macular degeneration. Ophthalmology **110**: 966-970.

Loukovaara S, V Lehtinen, R Nieminen & J Moilanen (2019): Topical levofloxacin, nepafenac and prednisolone acetate medication after cataract surgery in the biggest tertiary eye hospital in Finland during 2015-2018. Acta ophthalmologica **97**: e943-e945.

Lv X, W Li, Z Fang, X Xue & C Pan (2020): Periodontal Disease and Age-Related Macular Degeneration: A Meta-Analysis of 112,240 Participants. BioMed research international **2020**: 4753645.

Maller J, S George, S Purcell, J Fagerness, D Altshuler, MJ Daly & JM Seddon (2006): Common variation in three genes, including a noncoding variant in CFH, strongly influences risk of age-related macular degeneration. Nature genetics **38**: 1055-1059.

Mandelblum J, N Fischer, A Achiron, M Goldberg, R Tuuminen, E Zunz & O Spierer (2020): A Simple Pre-Operative Nuclear Classification Score (SPONCS) for Grading Cataract Hardness in Clinical Studies. Journal of clinical medicine **9**.

Marcus M, S Merin, M Wolf & M Feinsod (1983): Electrophysiologic tests in assessment of senile macular degeneration. Annals of ophthalmology **15**: 235-238.

Martin DF, MG Maguire, GS Ying, JE Grunwald, SL Fine & GJ Jaffe (2011): Ranibizumab and bevacizumab for neovascular age-related macular degeneration. The New England journal of medicine **364**: 1897-1908.

Merle BMJ, JM Colijn, A Cougnard-Grégoire, APM de Koning-Backus, MN Delyfer, JC Kiefte-de Jong, M Meester-Smoor, C Féart, T Verzijden, C Samieri, OH Franco, JF Korobelnik, CCW Klaver & C Delcourt (2019): Mediterranean Diet and Incidence of Advanced Age-Related Macular Degeneration: The EYE-RISK Consortium. Ophthalmology **126**: 381-390.

Michaud DS, Z Fu, J Shi & M Chung (2017): Periodontal Disease, Tooth Loss, and Cancer Risk. Epidemiologic reviews **39**: 49-58.

Midena E & E Pilotto (2017): Microperimetry in age: related macular degeneration. Eye (London, England) **31**: 985-994.

Miller DM, DG Espinosa-Heidmann, J Legra, SR Dubovy, IJ Sũner, DD Sedmak, RD Dix & SW Cousins (2004): The association of prior cytomegalovirus infection with neovascular age-related macular degeneration. American journal of ophthalmology **138**: 323-328.

Mimura T, H Funatsu, H Noma, M Shimura, Y Kamei, M Yoshida, A Kondo, E Watanabe & A Mizota (2019): Aqueous Humor Levels of Cytokines in Patients with Age-Related Macular Degeneration. Ophthalmologica. Journal international

d'ophtalmologie. International journal of ophthalmology. Zeitschrift fur Augenheilkunde **241**: 81-89.
Mitchell P, G Liew, B Gopinath & TY Wong (2018): Age-related macular degeneration. Lancet (London, England) **392**: 1147-1159.
Moisseiev J, A Alhalel, R Masuri & G Treister (1995): The impact of the macular photocoagulation study results on the treatment of exudative age-related macular degeneration. Archives of ophthalmology (Chicago, Ill. : 1960) **113**: 185-189.
Moja L, E Lucenteforte, KH Kwag, V Bertele, A Campomori, U Chakravarthy, R D'Amico, K Dickersin, L Kodjikian, K Lindsley, Y Loke, M Maguire, DF Martin, A Mugelli, B Mühlbauer, I Püntmann, B Reeves, C Rogers, C Schmucker, ML Subramanian & G Virgili (2014): Systemic safety of bevacizumab versus ranibizumab for neovascular age-related macular degeneration. The Cochrane database of systematic reviews **9**: Cd011230.
Mookhtiar M & L Downey (2012): Combined OCT and colour fundus photography in virtual clinic assessments of wet AMD patients. Eye (London, England) **26**: 619; author reply 620.
MPSG (1990): Krypton laser photocoagulation for idiopathic neovascular lesions. Results of a randomized clinical trial. Macular Photocoagulation Study Group. Archives of ophthalmology (Chicago, Ill. : 1960) **108**: 832-837.
MPSG (1993): Five-year follow-up of fellow eyes of patients with age-related macular degeneration and unilateral extrafoveal choroidal neovascularization. Macular Photocoagulation Study Group. Archives of ophthalmology (Chicago, Ill. : 1960) **111**: 1189-1199.
Munk MR, H Giannakaki-Zimmermann, L Berger, W Huf, A Ebneter, S Wolf & MS Zinkernagel (2017): OCT-angiography: A qualitative and quantitative comparison of 4 OCT-A devices. PloS one **12**: e0177059.
Müller H (1856): Anatomische Beiträge zur Ophthalmologie. Untersuchungen uber die Glasheute des Auges, Insbesondere die Glaslamelle der Choroidea und ihre senilen Veranderungen. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie **2**: 1-69.
Neelam K, J Nolan, U Chakravarthy & S Beatty (2009): Psychophysical function in age-related maculopathy. Survey of ophthalmology **54**: 167-210.
NEI (2019): Advanced AMD risk calculator. **https://www.nei.nih.gov/research/clinical-trials/age-related-eye-disease-study-2-areds2/advanced-amd-risk-calculator.**
Newman DK (2016): Photodynamic therapy: current role in the treatment of chorioretinal conditions. Eye (London, England) **30**: 202-210.
Niazi S, M Krogh Nielsen, A Singh, TL Sørensen & Y Subhi (2020): Prevalence of Charles Bonnet syndrome in patients with age-related macular degeneration: systematic review and meta-analysis. Acta ophthalmologica **98**: 121-131.
NKL Finnish Federation of Visually Impaired. **https://www.nkl.fi/en.**
Obana A, T Miki, K Hayashi, M Takeda, A Kawamura, T Mutoh, S Harino, I Fukushima, H Komatsu, Y Takaku & et al. (1994): Survey of complications of indocyanine green angiography in Japan. American journal of ophthalmology **118**: 749-753.
Ogura S, R Baldeosingh, IA Bhutto, SP Kambhampati, D Scott McLeod, MM Edwards, R Rais, W Schubert & GA Lutty (2020): A role for mast cells in geographic atrophy.

FASEB journal : official publication of the Federation of American Societies for Experimental Biology.
Ojamo M (2018): The Finnish Register of Visual Impairment, Annual Statistics 2018
Pagenstecher H GC (1875): Atlas der pathologischen anatomie des Augenpfels.
Palaska I, E Gagari & TC Theoharides (2016): The effects of P. gingivalis and E. coli LPS on the expression of proinflammatory mediators in human mast cells and their relevance to periodontal disease. Journal of biological regulators and homeostatic agents **30**: 655-664.
Pandey SK, EJ Milverton & AJ Maloof (2004): A tribute to Charles David Kelman MD: ophthalmologist, inventor and pioneer of phacoemulsification surgery. Clinical & experimental ophthalmology **32**: 529-533.
Pang CE & KB Freund (2014): Pachychoroid pigment epitheliopathy may masquerade as acute retinal pigment epitheliitis. Investigative ophthalmology & visual science **55**: 5252.
Pascolini D & SP Mariotti (2012): Global estimates of visual impairment: 2010. The British journal of ophthalmology **96**: 614-618.
Patel M & S Kiss (2014): Ultra-wide-field fluorescein angiography in retinal disease. Current opinion in ophthalmology **25**: 213-220.
Peng Q, N Visessook, DJ Apple, SK Pandey, L Werner, M Escobar-Gomez, R Schoderbek, KD Solomon & A Guindi (2000): Surgical prevention of posterior capsule opacification. Part 3: Intraocular lens optic barrier effect as a second line of defense. Journal of cataract and refractive surgery **26**: 198-213.
Pershing S, N Talwar, ST Armenti, J Grubbs, Jr., JM Rosenthal, VS Dedania & JD Stein (2019): Use of Bevacizumab and Ranibizumab for Wet Age-Related Macular Degeneration: Influence of CATT Results and Introduction of Aflibercept. American journal of ophthalmology **207**: 385-394.
Pitkänen L, P Tommila, K Kaarniranta, JE Jääskeläinen & K Kinnunen (2014): Retinal arterial macroaneurysms. Acta ophthalmologica **92**: 101-104.
Pockpa ZAD, X Struillou, D Kone, GS Mobio, A Soueidan & Z Badran (2019): Periodontal Diseases and Age-Related Macular Degeneration: Is There a Link? A Review. The Permanente journal **23**.
Porela-Tiihonen S, RP Roine, H Sintonen, K Kaarniranta, M Kokki & H Kokki (2016): Health-related quality of life after cataract surgery with the phacoemulsification technique and intraocular lens implantation. Acta ophthalmologica **94**: 21-25.
Providência J, TM Rodrigues, M Oliveira, J Bernardes, JP Marques, J Murta & R Silva (2018): Real-World Results of Aflibercept versus Ranibizumab for the Treatment of Exudative AMD Using a Fixed Regimen. BioMed research international **2018**: 9276580.
Puertas A, A Magan-Fernandez, V Blanc, L Revelles, F O'Valle, E Pozo, R León & F Mesa (2018): Association of periodontitis with preterm birth and low birth weight: a comprehensive review. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet **31**: 597-602.
Rasmussen A, SB Bloch, J Fuchs, LH Hansen, M Larsen, M LaCour, H Lund-Andersen & B Sander (2013): A 4-year longitudinal study of 555 patients treated with

ranibizumab for neovascular age-related macular degeneration. Ophthalmology **120**: 2630-2636.
Regillo CD (1999): The present role of indocyanine green angiography in ophthalmology. Current opinion in ophthalmology **10**: 189-196.
Riaz Y, JS Mehta, R Wormald, JR Evans, A Foster, T Ravilla & T Snellingen (2006): Surgical interventions for age-related cataract. The Cochrane database of systematic reviews **2006**: Cd001323.
Ridley H (1954): Further experiences of intra-ocular acrylic lens surgery; with a report of more than 100 cases. The British journal of ophthalmology **38**: 156-162.
Rim TH, CY Cheng, DW Kim, SS Kim & TY Wong (2017): A nationwide cohort study of cigarette smoking and risk of neovascular age-related macular degeneration in East Asian men. The British journal of ophthalmology **101**: 1367-1373.
Roberts HW, AC Day & DP O'Brart (2020): Femtosecond laser-assisted cataract surgery: A review. European journal of ophthalmology **30**: 417-429.
Roh M, I Laíns, HJ Shin, DH Park, S Mach, DG Vavvas, IK Kim, JW Miller, D Husain & JB Miller (2019): Microperimetry in age-related macular degeneration: association with macular morphology assessed by optical coherence tomography. The British journal of ophthalmology **103**: 1769-1776.
Rong X, W He, Q Zhu, D Qian, Y Lu & X Zhu (2019): Intraocular lens power calculation in eyes with extreme myopia: Comparison of Barrett Universal II, Haigis, and Olsen formulas. Journal of cataract and refractive surgery **45**: 732-737.
Roquet W, F Roudot-Thoraval, G Coscas & G Soubrane (2004): Clinical features of drusenoid pigment epithelial detachment in age related macular degeneration. The British journal of ophthalmology **88**: 638-642.
Rosenfeld PJ, DM Brown, JS Heier, DS Boyer, PK Kaiser, CY Chung & RY Kim (2006): Ranibizumab for neovascular age-related macular degeneration. The New England journal of medicine **355**: 1419-1431.
Sarraf D, A Joseph & E Rahimy (2014): Retinal pigment epithelial tears in the era of intravitreal pharmacotherapy: risk factors, pathogenesis, prognosis and treatment (an American Ophthalmological Society thesis). Transactions of the American Ophthalmological Society **112**: 142-159.
Sarwar H & N Modi (2014): Sir Harold Ridley: innovator of cataract surgery. Journal of perioperative practice **24**: 210-212.
Schmidt-Erfurth U, S Klimscha, SM Waldstein & H Bogunović (2017): A view of the current and future role of optical coherence tomography in the management of age-related macular degeneration. Eye (London, England) **31**: 26-44.
Schwartz SG & CT Leffler (2014): Uses of the word "macula" in written English, 1400-present. Survey of ophthalmology **59**: 649-654.
Schwarz F, J Derks, A Monje & HL Wang (2018): Peri-implantitis. Journal of periodontology **89 Suppl 1**: S267-s290.
Seddon JM, J Cote & B Rosner (2003): Progression of age-related macular degeneration: association with dietary fat, transunsaturated fat, nuts, and fish intake. Archives of ophthalmology (Chicago, Ill. : 1960) **121**: 1728-1737.
Seddon JM, S George, B Rosner & N Rifai (2005): Progression of age-related macular degeneration: prospective assessment of C-reactive protein, interleukin 6, and other cardiovascular biomarkers. Archives of ophthalmology (Chicago, Ill. : 1960) **123**: 774-782.

Seddon JM, RE Silver & B Rosner (2016): Response to AREDS supplements according to genetic factors: survival analysis approach using the eye as the unit of analysis. The British journal of ophthalmology **100**: 1731-1737.
Seitsonen S, I Järvelä, S Meri, P Tommila, P Ranta & I Immonen (2008): Complement factor H Y402H polymorphism and characteristics of exudative age-related macular degeneration lesions. Acta ophthalmologica **86**: 390-394.
Shin YU, HW Lim, EH Hong, MH Kang, M Seong, E Nam & H Cho (2017): The association between periodontal disease and age-related macular degeneration in the Korea National health and nutrition examination survey: A cross-sectional observational study. Medicine **96**: e6418.
Skeie JM, JH Fingert, SR Russell, EM Stone & RF Mullins (2010): Complement component C5a activates ICAM-1 expression on human choroidal endothelial cells. Investigative ophthalmology & visual science **51**: 5336-5342.
Smith W, P Mitchell & SR Leeder (1996): Smoking and age-related maculopathy. The Blue Mountains Eye Study. Archives of ophthalmology (Chicago, Ill. : 1960) **114**: 1518-1523.
Smith W, P Mitchell & SR Leeder (2000): Dietary fat and fish intake and age-related maculopathy. Archives of ophthalmology (Chicago, Ill. : 1960) **118**: 401-404.
Sochocka M, K Zwolińska & J Leszek (2017): The Infectious Etiology of Alzheimer's Disease. Current neuropharmacology **15**: 996-1009.
Starr MR, MA Mahr, AJ Barkmeier, R Iezzi, WM Smith & SJ Bakri (2018): Outcomes of Cataract Surgery in Patients With Exudative Age-related Macular Degeneration and Macular Fluid. American journal of ophthalmology **192**: 91-97.
Stopa M, BA Bower, E Davies, JA Izatt & CA Toth (2008): Correlation of pathologic features in spectral domain optical coherence tomography with conventional retinal studies. Retina (Philadelphia, Pa.) **28**: 298-308.
Subhi Y, M Krogh Nielsen, CR Molbech, A Oishi, A Singh, MH Nissen & TL Sørensen (2019): Plasma markers of chronic low-grade inflammation in polypoidal choroidal vasculopathy and neovascular age-related macular degeneration. Acta ophthalmologica **97**: 99-106.
Sun KT, NY Hsia, SC Chen, CL Lin, IA Chen, IT Wu, K Palanisamy, TC Shen & CY Li (2019): RISK OF AGE-RELATED MACULAR DEGENERATION IN PATIENTS WITH PERIODONTITIS: A Nationwide Population-Based Cohort Study. Retina (Philadelphia, Pa.).
Suominen-Taipale L NA, Vehkalahti M, Aromaa, A, eds. (2008): Oral Health in Adult Finnish Population. Health 2000 Survey. Publications of the National Public Health Institute, Helsinki, Finland. **B25/2008. Helsinki, Finland: National Public Health Institute.**
Taieb A (1955): [From Casanova's memories to Ridley's operation]. Archives d'ophtalmologie et revue generale d'ophtalmologie **15**: 501-503.
Taipale C, JM Lindholm, I Laine & R Tuuminen (2020): Comparison of two different treat-and-extend protocols with aflibercept in wet age-related macular degeneration. Acta ophthalmologica **98**: 267-273.
Takasago Y, C Shiragami, M Kobayashi, R Osaka, A Ono, A Yamashita, A Tsujikawa & K Hirooka (2019): MACULAR ATROPHY FINDINGS BY OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY COMPARED WITH FUNDUS

AUTOFLUORESCENCE IN TREATED EXUDATIVE AGE-RELATED MACULAR DEGENERATION. Retina (Philadelphia, Pa.) **39**: 296-302.
Tammela T, G Zarkada, E Wallgard, A Murtomäki, S Suchting, M Wirzenius, M Waltari, M Hellström, T Schomber, R Peltonen, C Freitas, A Duarte, H Isoniemi, P Laakkonen, G Christofori, S Ylä-Herttuala, M Shibuya, B Pytowski, A Eichmann, C Betsholtz & K Alitalo (2008): Blocking VEGFR-3 suppresses angiogenic sprouting and vascular network formation. Nature **454**: 656-660.
Tan ACS, D Simhaee, C Balaratnasingam, KK Dansingani & LA Yannuzzi (2016): A Perspective on the Nature and Frequency of Pigment Epithelial Detachments. American journal of ophthalmology **172**: 13-27.
TAP (1999): Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials--TAP report. Treatment of age-related macular degeneration with photodynamic therapy (TAP) Study Group. Archives of ophthalmology (Chicago, Ill. : 1960) **117**: 1329-1345.
Timoney PJ & CS Breathnach (2013): Allvar Gullstrand and the slit lamp 1911. Irish journal of medical science **182**: 301-305.
Tonetti MS, H Greenwell & KS Kornman (2018): Staging and grading of periodontitis: Framework and proposal of a new classification and case definition. Journal of periodontology **89 Suppl 1**: S159-s172.
Tonetti MS & TE Van Dyke (2013): Periodontitis and atherosclerotic cardiovascular disease: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. Journal of periodontology **84**: S24-29.
Tsai ASH, N Cheung, ATL Gan, GJ Jaffe, S Sivaprasad, TY Wong & CMG Cheung (2017): Retinal angiomatous proliferation. Survey of ophthalmology **62**: 462-492.
Tuuminen R, A Tuulonen & K Kaarniranta (2017): The Finnish national guideline for diagnosis, treatment and follow-up of patients with wet age-related macular degeneration. Acta ophthalmologica **95**: 649-650.
Tyagi P, Z Juma, YK Hor, NW Scott, A Ionean & C Santiago (2018): Clinical response of pigment epithelial detachment associated with neovascular age-related macular degeneration in switching treatment from Ranibizumab to Aflibercept. BMC ophthalmology **18**: 148.
Verhoeff FH & HP Grossman (1937): The Pathogenesis of Disciform Degeneration of the Macula. Transactions of the American Ophthalmological Society **35**: 262-294.
Vitkov L, LE Muñoz, J Knopf, C Schauer, H Oberthaler, B Minnich, M Hannig & M Herrmann (2021): Connection between Periodontitis-Induced Low-Grade Endotoxemia and Systemic Diseases: Neutrophils as Protagonists and Targets. International journal of molecular sciences **22**.
Vottonen P, A Pääkkönen, IM Tarkka & K Kaarniranta (2015): Best-corrected visual acuity and retinal thickness are associated with improved cortical visual processing in treated wet AMD patients. Acta ophthalmologica **93**: 621-625.
Vuori ML & M Mäntyjärvi (2006): Colour vision and retinal nerve fibre layer photography in patients with an Acrysof Natural intraocular lens. Acta ophthalmologica Scandinavica **84**: 92-94.
Wagley S, KV Marra, RA Salhi, S Gautam, R Campo, P Veale, J Veale & JG Arroyo (2015): PERIODONTAL DISEASE AND AGE-RELATED MACULAR DEGENERATION:

Results From the National Health and Nutrition Examination Survey III. Retina (Philadelphia, Pa.) **35**: 982-988.
Walland MJ (2017): Of emperors and clothes: why FLACS? Clinical & experimental ophthalmology **45**: 221-223.
Wang CJ & LK McCauley (2016): Osteoporosis and Periodontitis. Current osteoporosis reports **14**: 284-291.
Wang X, T Sawada, O Sawada, Y Saishin, P Liu & M Ohji (2014): Serum and plasma vascular endothelial growth factor concentrations before and after intravitreal injection of aflibercept or ranibizumab for age-related macular degeneration. American journal of ophthalmology **158**: 738-744.e731.
Warwick A & A Lotery (2018): Genetics and genetic testing for age-related macular degeneration. Eye (London, England) **32**: 849-857.
Wedell-Neergaard AS, L Eriksen, M Grønbæk, BK Pedersen, R Krogh-Madsen & J Tolstrup (2018): Low fitness is associated with abdominal adiposity and low-grade inflammation independent of BMI. PloS one **13**: e0190645.
WHO (2019): Blindness and Visual Impairment. **https://www.who.int/news-room/fact-sheets/detail/blindness-and-visual-impairment**.
Wong WL, X Su, X Li, CM Cheung, R Klein, CY Cheng & TY Wong (2014): Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. The Lancet. Global health **2**: e106-116.
Woo SJ, J Ahn, MA Morrison, SY Ahn, J Lee, KW Kim, MM DeAngelis & KH Park (2015): Analysis of Genetic and Environmental Risk Factors and Their Interactions in Korean Patients with Age-Related Macular Degeneration. PloS one **10**: e0132771.
Wu J & X Sun (2019): Complement system and age-related macular degeneration: drugs and challenges. Drug design, development and therapy **13**: 2413-2425.
Yaacob M, HV Worthington, SA Deacon, C Deery, AD Walmsley, PG Robinson & AM Glenny (2014): Powered versus manual toothbrushing for oral health. The Cochrane database of systematic reviews **2014**: Cd002281.
Yannuzzi (1982): Idiopathic Polypoidal Choroidal Vasculopathy. Macula Society Meeting. Miami, FL, USA: February 5, 1982.
Yannuzzi LA (1982): A modified Amsler grid. A self-assessment test for patients with macular disease. Ophthalmology **89**: 157-159.
Ylinen P, C Taipale, JM Lindholm, I Laine, E Holmström & R Tuuminen (2018): Postoperative management in cataract surgery: nepafenac and preservative-free diclofenac compared. Acta ophthalmologica **96**: 853-859.
Zaldivar R, MC Shultz, JM Davidorf & JT Holladay (2000): Intraocular lens power calculations in patients with extreme myopia. Journal of cataract and refractive surgery **26**: 668-674.
Zaret MM, GM Breinin, H Schmidt, H Ripps, IM Siegel & LR Solon (1961): Ocular lesions produced by an optical maser (laser). Science (New York, N.Y.) **134**: 1525-1526.
Zerbib J, C Delcourt, N Puche, G Querques, SY Cohen, J Sahel, JF Korobelnik, M Le Goff & EH Souied (2014): Risk factors for exudative age-related macular degeneration in a large French case-control study. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie **252**: 899-907.

Zhang QY, LJ Tie, SS Wu, PL Lv, HW Huang, WQ Wang, H Wang & L Ma (2016): Overweight, Obesity, and Risk of Age-Related Macular Degeneration. Investigative ophthalmology & visual science **57**: 1276-1283.

Zhao Y, J Li, W Lu, P Chang, P Lu, F Yu, X Xing, X Ding, F Lu & Y Zhao (2013): Capsular adhesion to intraocular lens in highly myopic eyes evaluated in vivo using ultralong-scan-depth optical coherence tomography. American journal of ophthalmology **155**: 484-491.e481.